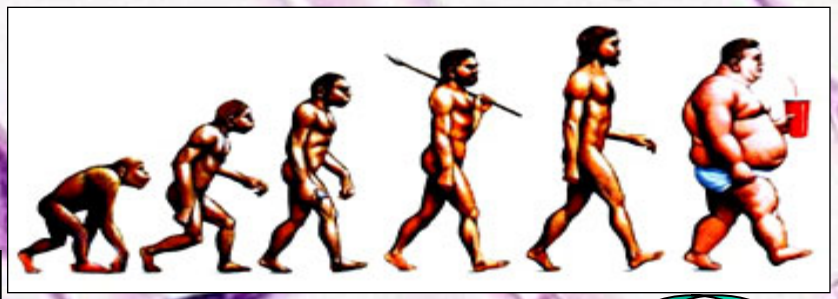
Obesity : not just a matter of food

ARNOULD Thierry
University of Namur
May 19, EFID 2016

Less than 30 years
Evolution ???



Homo sapiens sapiens

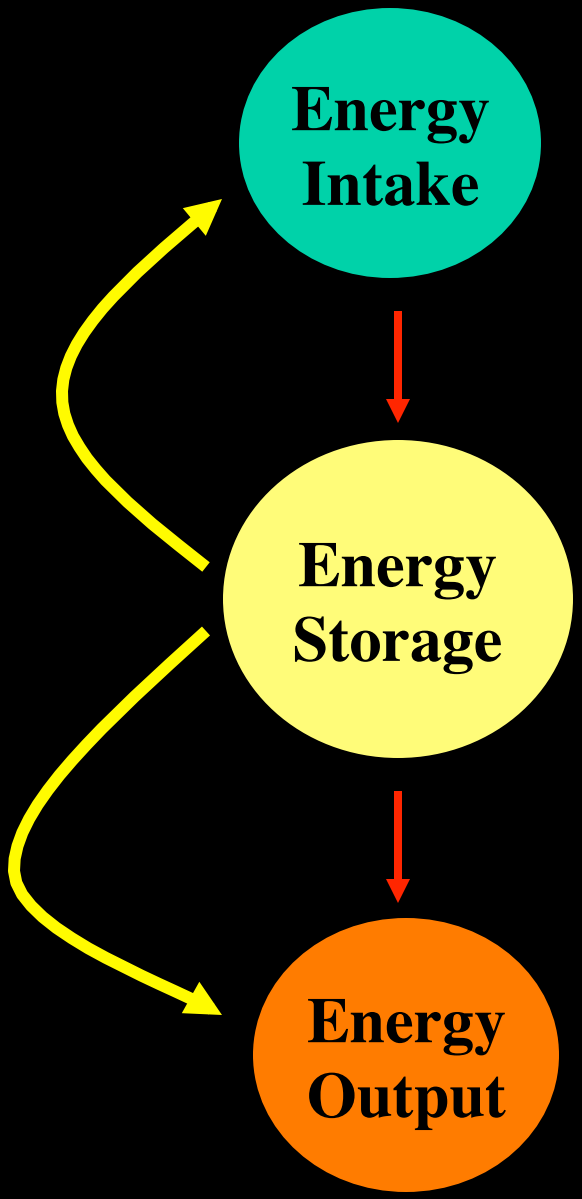
Homo sapiens obesus diabeticus

Unité de Recherche en Biologie Cellulaire (URBC)
NAmur Research Institute for LIfe Sciences (NARILIS)
University of Namur

Obesity : a multifactorial problem

What is your problem buddy ?

Your food ? Your genes ? Your epigenetics? Your brain ? Your life style? Your microbiota?...



Obesity

1. Obesity : definition, epidemiology, distribution
2. The role of the brain and CNS in food intake control
3. Obesity and associated diseases : co-morbidities
4. Adipose tissues and their role in obesity
5. Genetic control of body mass
6. The importance of the microbiota
7. Thermoregulation and UCPs : an energy dissipating mechanism
8. Management of obesity

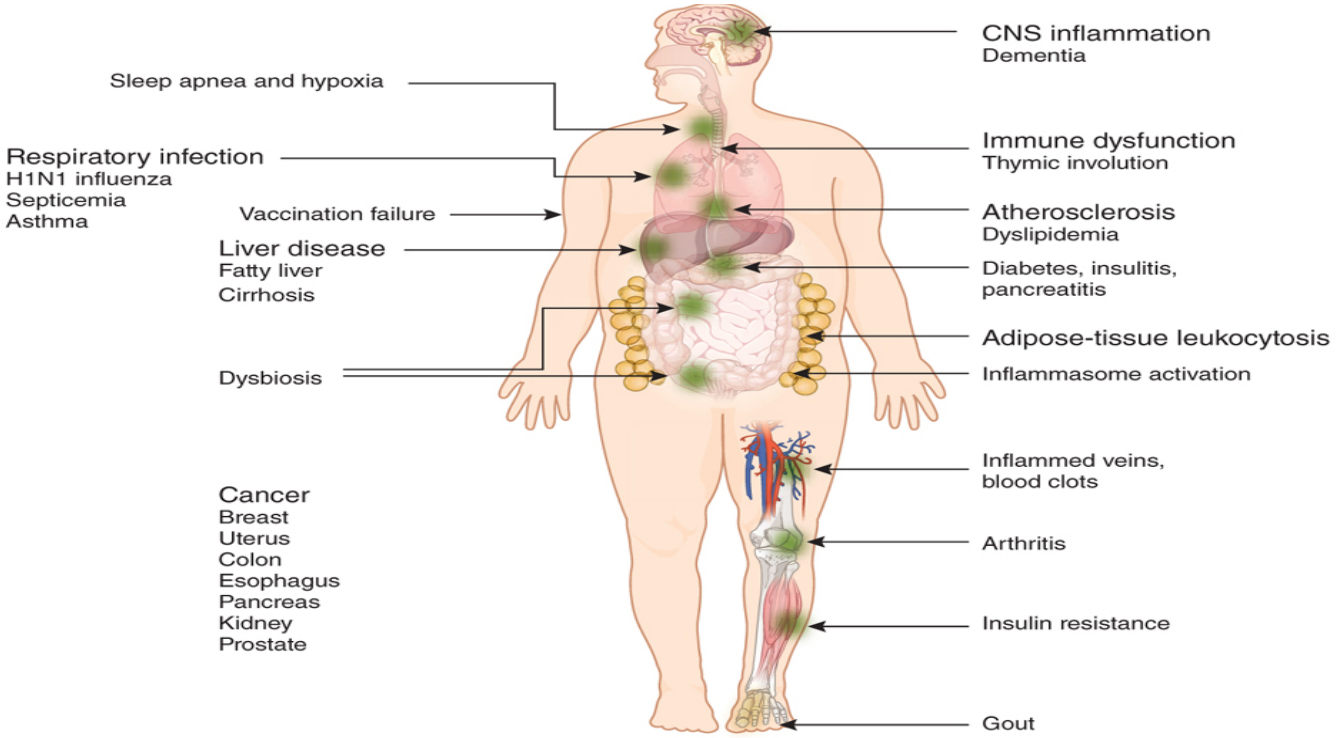
The Healthcare Costs of Obesity

Obesity is one of the biggest drivers of preventable chronic diseases and healthcare costs in the United States. Currently, estimates for these costs range from $147 billion to nearly $210 billion per year.[1] In addition, obesity is associated with job absenteeism, costing approximately $4.3 billion annually[2] and with lower productivity while at work, costing employers $506 per obese worker per year.[3]

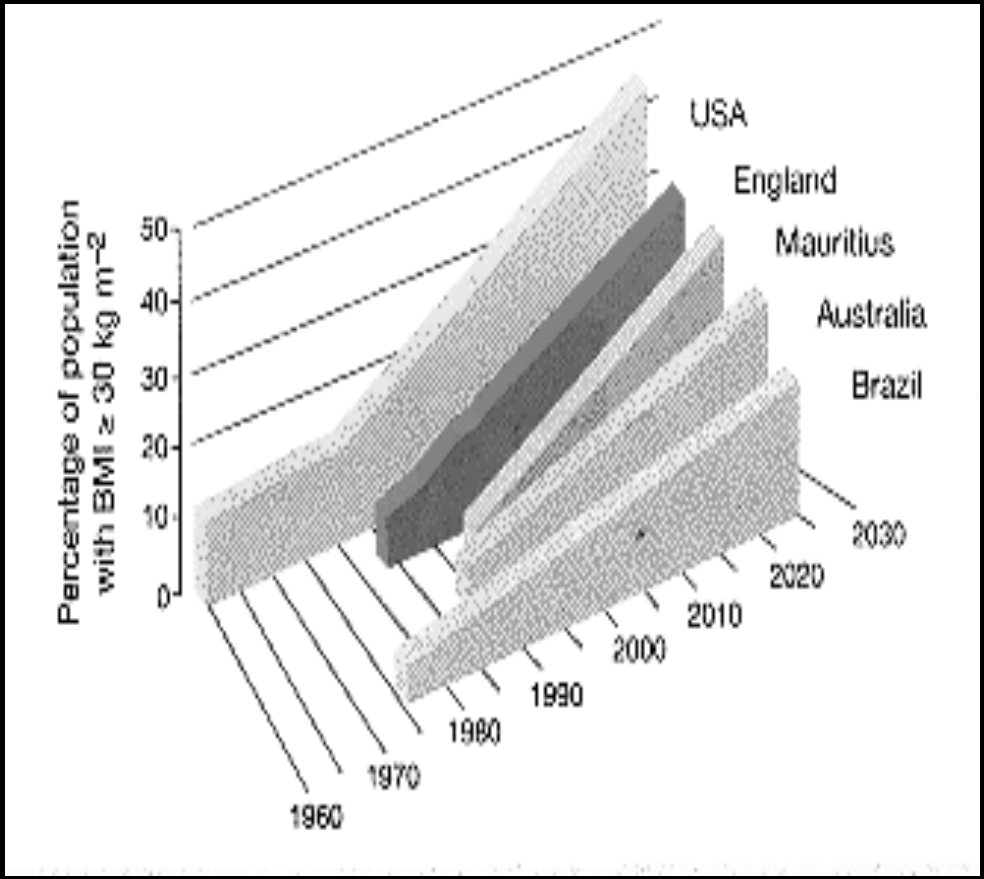
http://stateofobesity.org/healthcare-costs-obesity/

Metabolic syndrome:

- Hypertriglyceridemia
- Increased LDL level
- Decreased HDL level
- Hypertension
- Hyperglycemia
- Insulin resistance



Obesity in the world : increases and affects childs



Historic, current and projection for obesity prevalence

(International Obesity Task Force)

Average O/OW in adult populations :

USA : > 66 % (2014)

> 2 in 3 adults are overweight or obese.

- > 33 % of adults are obese.
- > 5 % of adults are extremely obese.
- > 1/3 of children and adolescents ages 6 to 19 are considered to be overweight or obese.
- > 1 in 6 children and adolescents ages 6 to 19 are considered to be obese.

EU : 37-56% F and 51-69% M (2010)
(Roumania : 15% lower versus UK)

Rapid growth…

UK : 6 % H (80) --->17 % (97)
8 % F (80) ---> 20 % (97)

Asia : Japan-China : increasing but lower

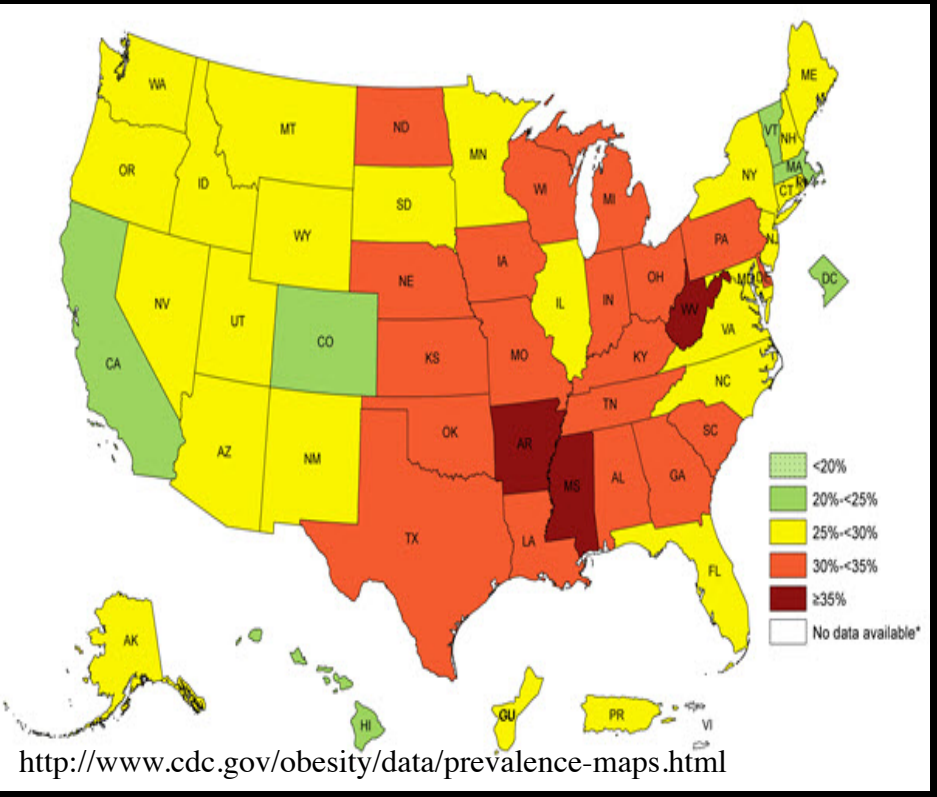
Globesity

International classification of underweight, normal range, overweight and obese adults (BMI/WHO, 2004)

Classification	BMI (kg/m^2)	
	Principal cut-off points	Additional cut-off points
Underweight	<18.50	<18.50
Severe thinness	<16.00	<16.00
Moderate thinness	16.00-16.99	16.00-16.99
Mild thinness	17.00-18.49	17.00-18.49
Normal range	18.50-24.99	18.50-22.99
		23.00-24.99
Overweight	≥ 25.00	≥ 25.00
Pre-obese	25.00-29.99	25.00-27.49
		27.50-29.99
Obese	≥ 30.00	≥ 30.00
Obese class I	30.00-34.99	30.00-32.49
		32.50-34.99
Obese class II	35.00-39.99	35.00-37.49
		37.50-39.99
Obese class III	≥ 40.00	≥ 40.00

Obesity and overweight classificiation: BMI
The shift from fat to carbohydrates ? *(Science 291 (2001) : 2536)*

BMI / IMC :mass (Kg) / [height (m)]^2 ≥ 30
---> > 35 % in the US (Coca-Colanized countries)
---> > 60 % are obese or overweight



http://www.cdc.gov/obesity/data/prevalence-maps.html

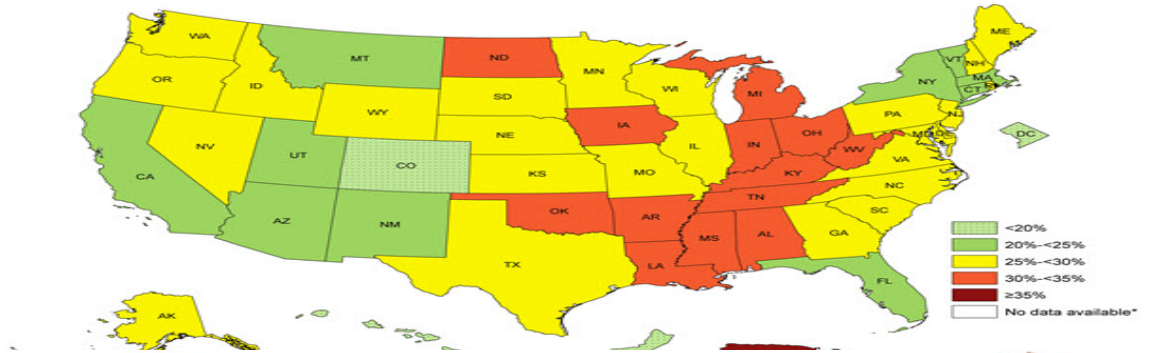
1958 : first textbook on cholesterol-
The low-fat gospel :"In America, we no longer fear God or the Communists, but we fear fat"
(D. Kritechvsky- Winstar Institute)

Classification of overweight (WHO experts)		
BMI (Kg/m2)	**WHO**	**Popular**
< 18.5	**UW**	**thin**
18.5-24.9	**N**	**healthy**
25-29.9	**G1/ OW**	**overweight**
30.0-39.9	**G2/ OW**	**obesity**
≥ 40	**G3/ OW**	**morbid obesity**

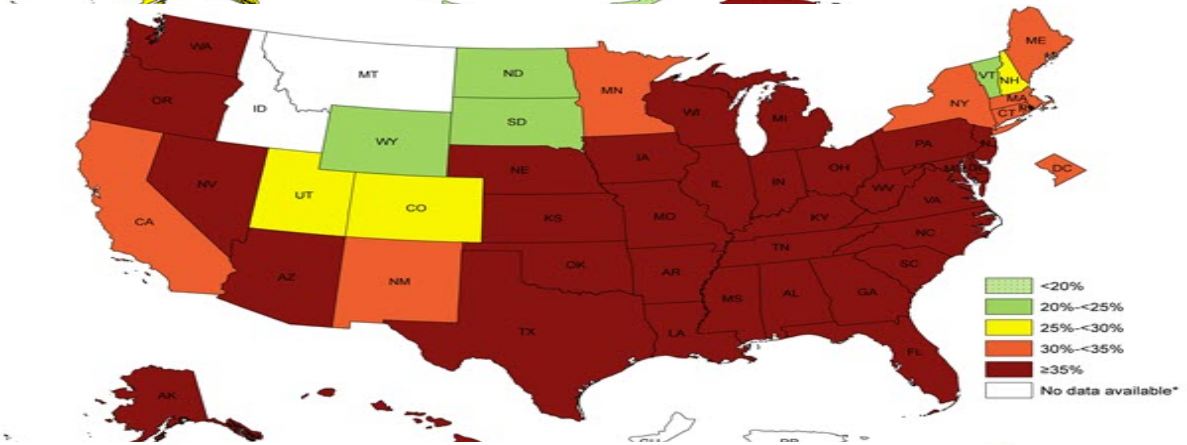
Obesity prevalence in 2014

No state had a prevalence of obesity less than 20%.
5 states and the District of Columbia had a prevalence of obesity between 20% and <25%.
23 states, Guam and Puerto Rico had a prevalence of obesity between 25% and <30%.
19 states had a prevalence of obesity between 30% and <35%.
3 states (Arkansas, Mississippi and West Virginia) had a prevalence of obesity of 35% or greater.

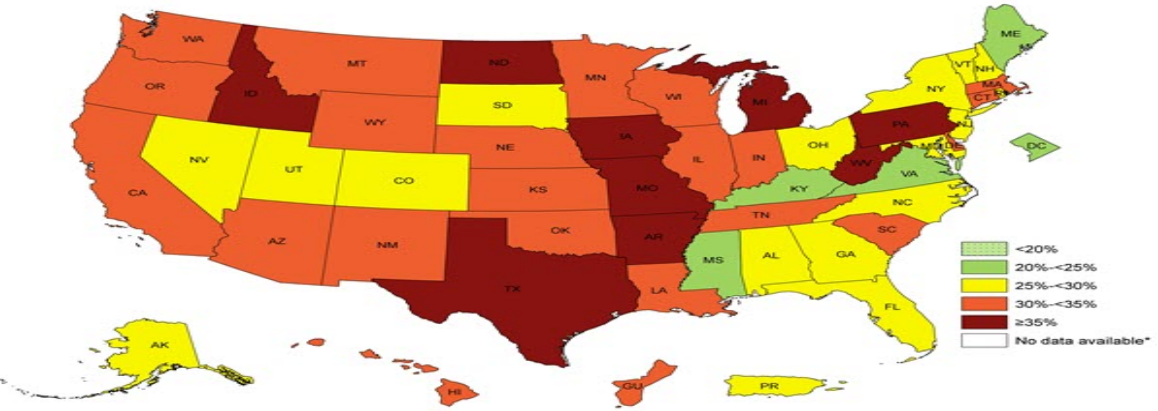
Are we all equals ?



Whites



Blacks



Hispanics

Fat distribution influences obesity-associated diseases

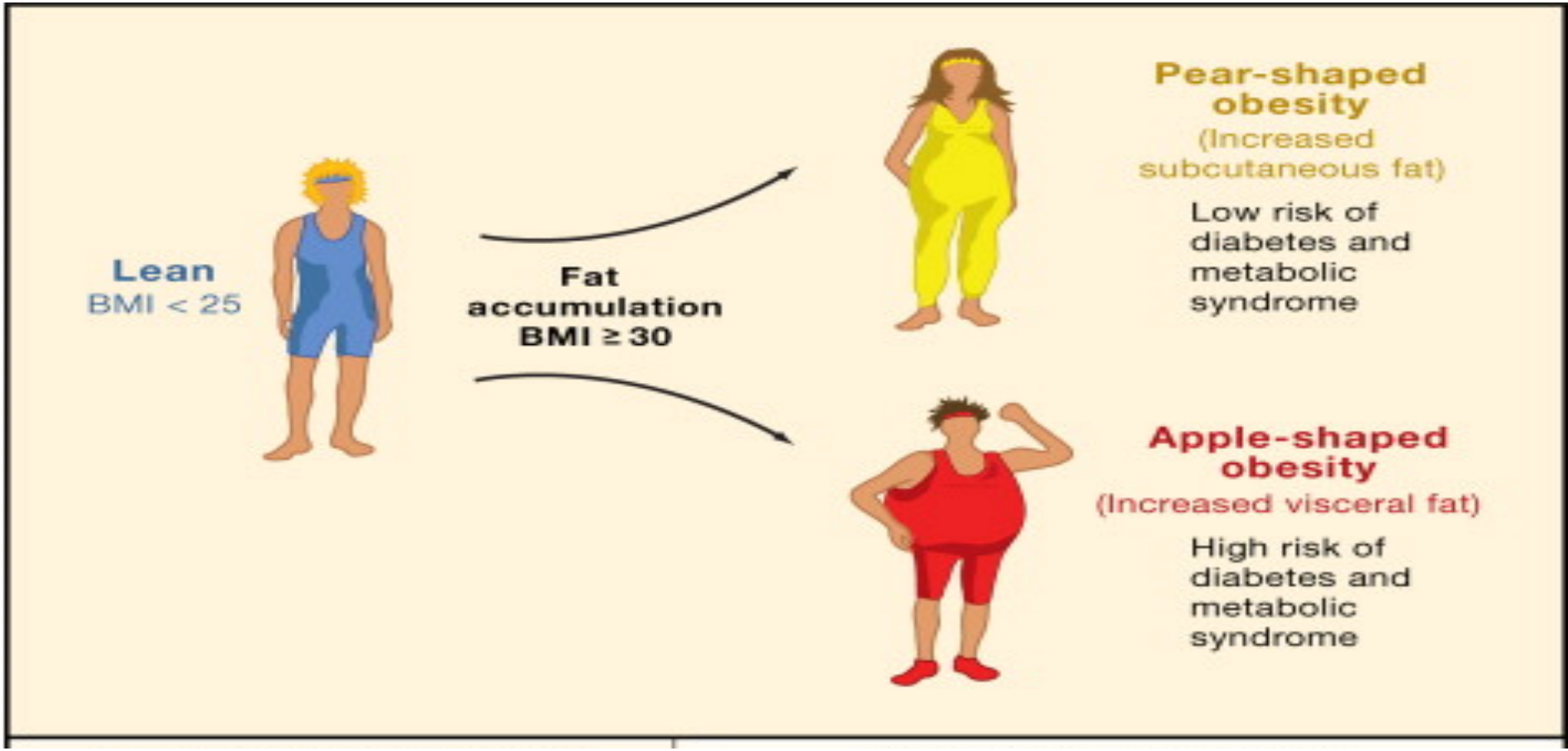
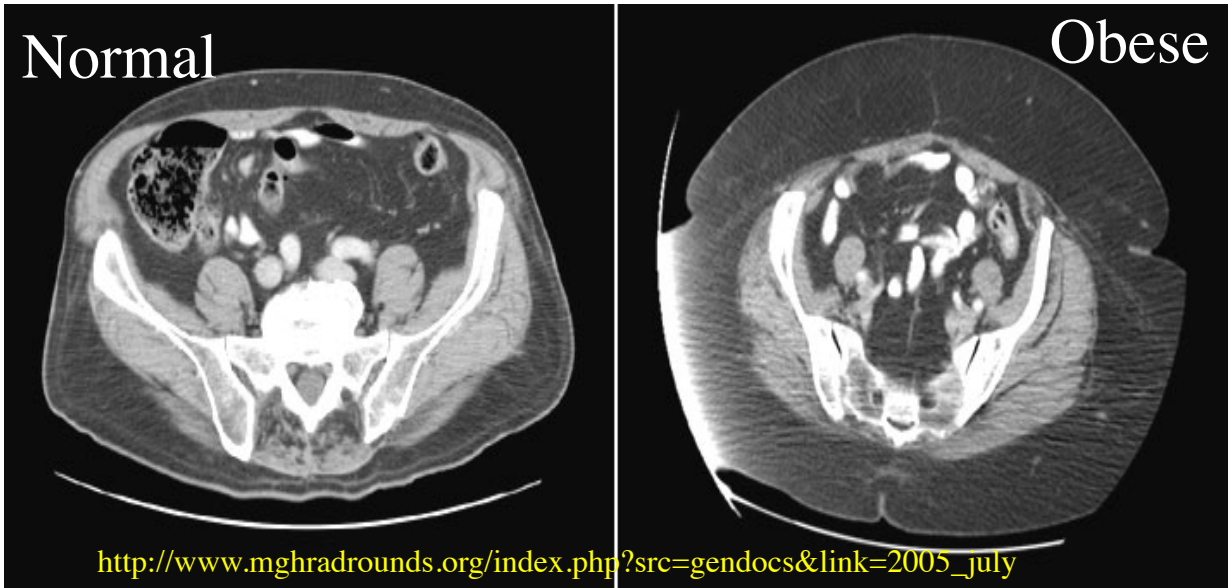
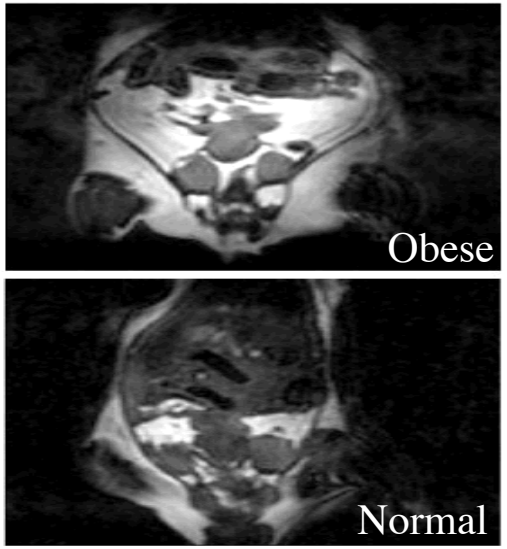


Figure 4: Fat distribution Influences. Fat distribution can be estimated by measurements of the ratio of waist to the hip circumference (WHR). Obese people with low WHR (subcutaneous or pear-shaped obesity) are at low risk for metabolic complications of obesity, whereas people with high WHR (visceral or apple-shaped obesity) are at high risk for these complications (based on Gesta *et al.*, 2007).

How to determine obesity?

- BMI : ≥ 30 kg/m^2
- Waist circumference (WC) : > 90 cm
- Waist-to-hip ratio (WHR) : ≥ 0.9
- Waist-to-height (WHtR) : > 0.5
- MRI : Abdominal CT images





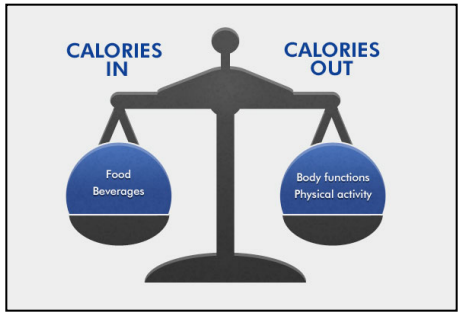
Obesity is a complex and most likely multifactorial state

UNIVERSITÉ DE NAMUR

narilis Namur Research Institute for Life Sciences

Environmental factors → **OBESITY** ← Genetic factors

- **Energy absorption/intake**
  - Food consumption
  - Type of food
- **Energy consumption/expenditure**
  - Less physical exercice
  - Less mobility due to work ?



- **Monogenic/polygenic causes**
  - Deletion/mutation
  - Polymorphisms
  - Epigenetics
  - Susceptibility genes

  (97 variants : metabolism and brain control of food intake)

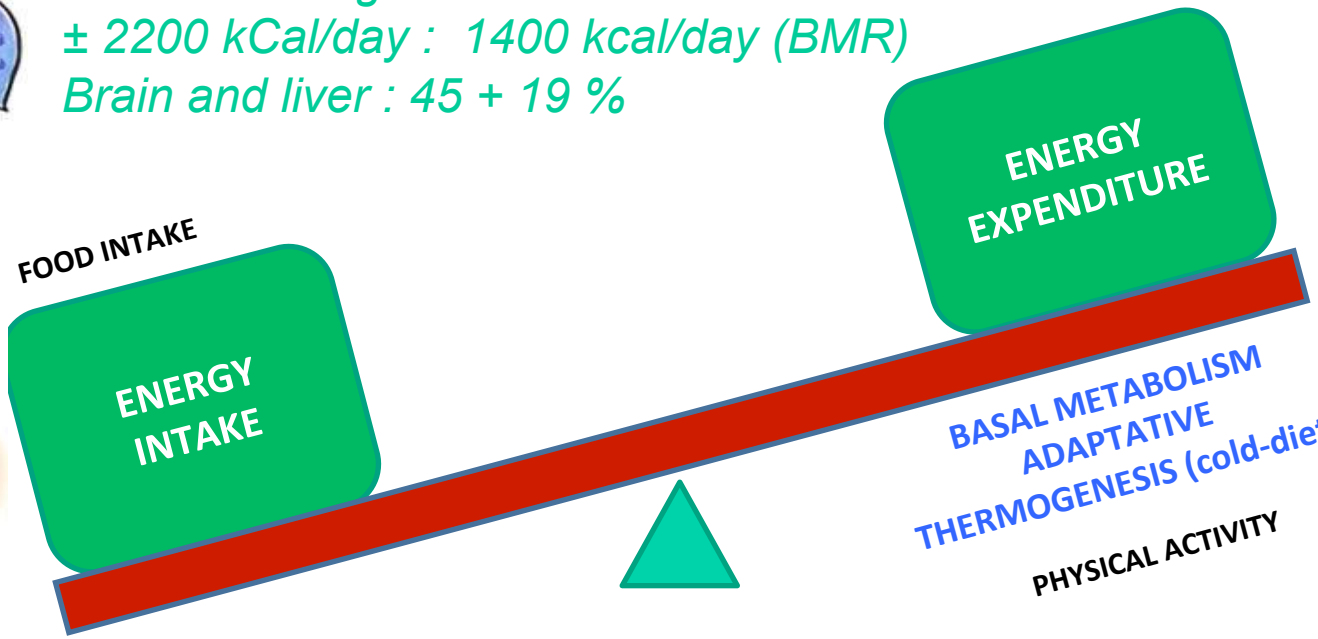
Metabolism

Microbial factors
- **Gut microbiota**

Cultural Psychological factors

Energy balance and unbalance system
What Does Cause Obesity?

A man of 70 kg :
± 2200 kCal/day : 1400 kcal/day (BMR)
Brain and liver : 45 + 19 %



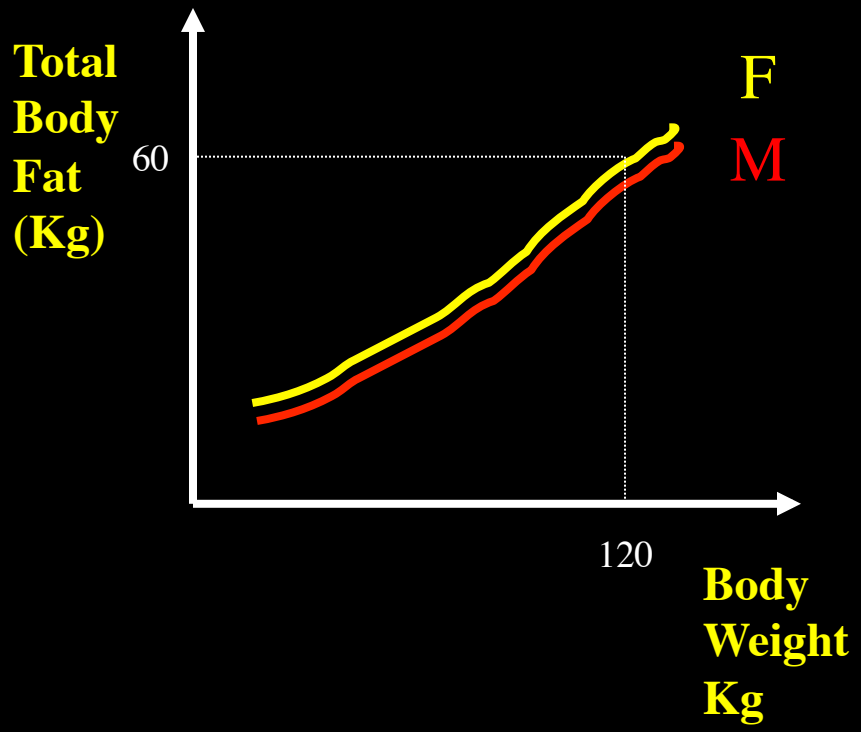
Risk factors:
•Genetic background
•Lifestyle
•Environment (foetal programming and maternal undernutrition)
•Gut microbiota

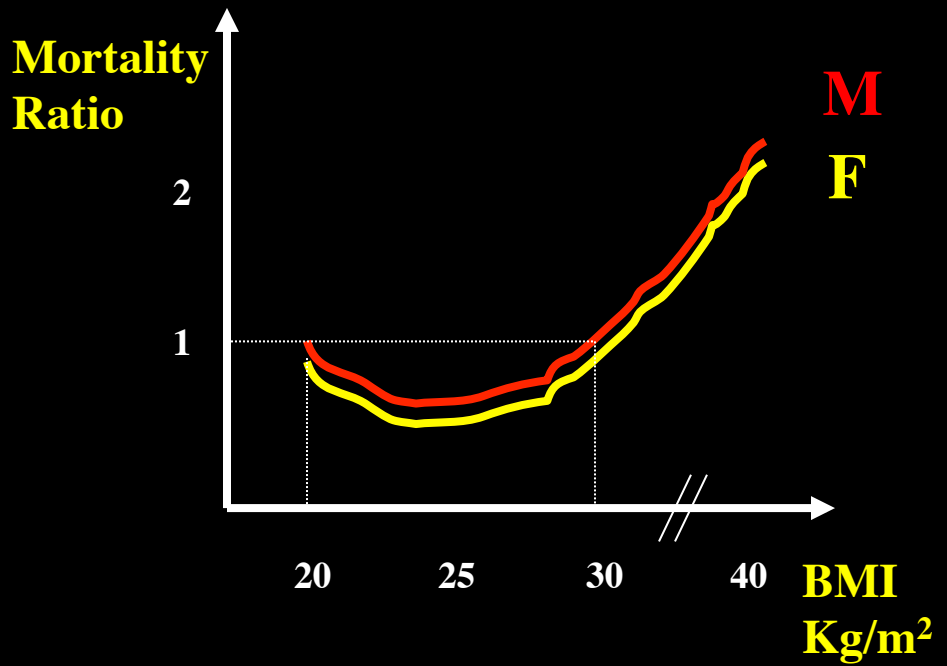
Obesity ➡ Excessive accumulation of adipose tissue

Increase in fat cell volume (hypertrophy) and/or the number of adipose cells (hyperplasia)

Life expectancy decreases when BMI increases

Person of 70 kg : 15 kg of fat in adipose tissues





Organ	Mass (g)	En (Kcal)
Fat (AT)	15.000	140.000
Proteins (M)	6000	24.000
Glycogen (M)	400	1600
Glycogen (L)	80	320

Fuel reservoirs of a normal 70 kg man after overnight fasting

« We are what we eat »
« Why do we need to eat? What ? and How much…?

TABLEAU 2.1 Éléments naturels entrant dans la composition du corps humain

Symbole chimique	Élément	Numéro atomique (voir la p. 30)	Pourcentage de la masse corporelle
O	Oxygène	8	65,0
C	Carbone	6	18,5
H	Hydrogène	1	9,5
N	Azote	7	3,3
Ca	Calcium	20	1,5
P	Phosphore	15	1,0
K	Potassium	19	0,4
S	Soufre	16	0,3
Na	Sodium	11	0,2
Cl	Chlore	17	0,2
Mg	Magnésium	12	0,1

Autres éléments à l'état de trace (moins de 0,01 %) : bore (B), chrome (Cr), cobalt (Co), cuivre (Cu), fluor (F), iode (I), fer (Fe), manganèse (Mn), molybdène (Mo), sélénium (Se), silicium (Si), étain (Sn), vanadium (V) et zinc (Zn).

C, O, H, N = 96 %

Ca, P, S, K, Na, Cl, Mg = ± 4 %

Trace elements : but essentials

Fe : essential

I : Thryroxine

B, Cr, Co, Cu, F, Mn, Mo, Se,…

Quantitative and Qualitative aspects of food :

Proteins

Lipids

Carbohydrates

Nucleic acids : almost no contribution to fuels

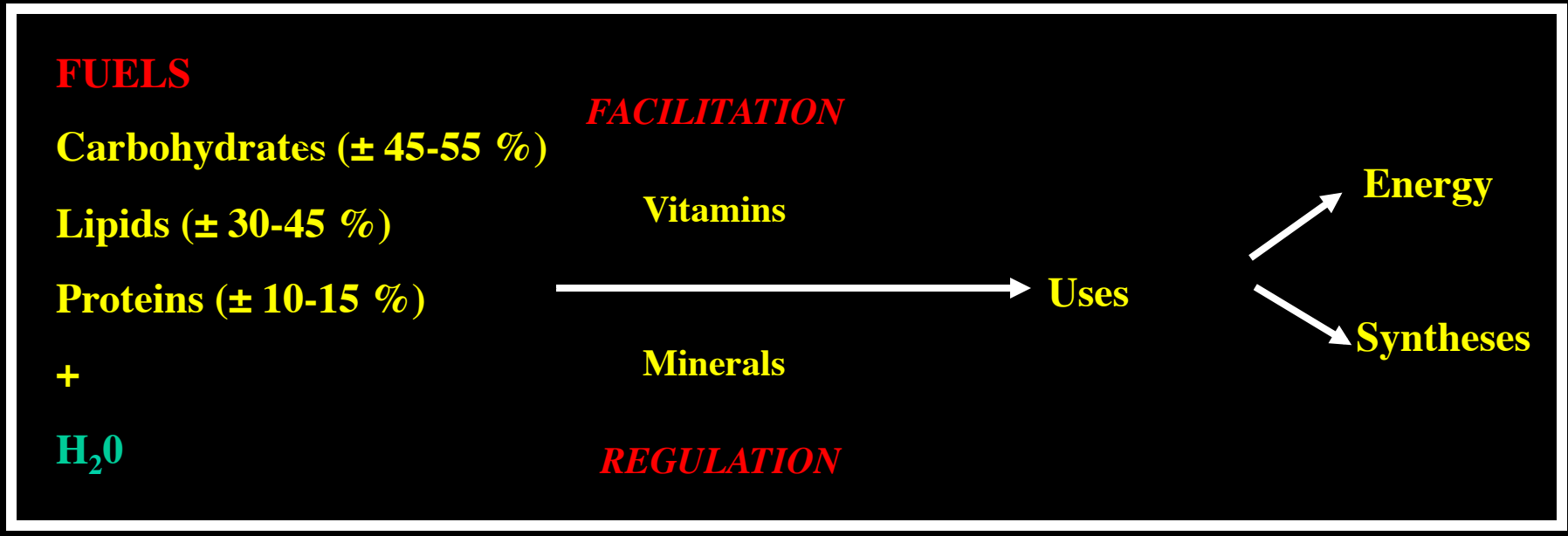
« If not enough...or too much...or too much of some…

--> Impair Functions --> Diseases

- **Optimal life : healthy lifespan**
- **Optimal capacity : physical and intellectual**

« lower calorie diet »

Energy and Syntheses



Energy expenditures :

Basal Metabolism at Rest (BMR)

Growth, Repair, Syntheses, Reproduction…Turn-over

Physical activity

Heat production : Mitochondrial Uncoupling

WHO : « *If you eat to much of one thing, you eat a lot less of something else. So for every theory saying that this disease is caused by an excess of x, you can produce an alternative theory saying it is a deficiency in y* ».

Structures of FFA and sugars

1 Palmitic 16

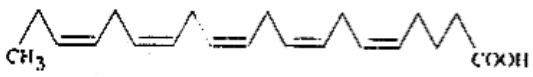
Stearic 18

Oleic 18 (n-9)

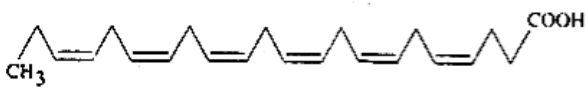
Linolenic 18 (n-3)

Linoleic 18 (n-6)

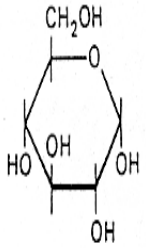
Polyunsaturated fatty acids are often classified into 'families' depending on the position of the first double bond counting back from the methyl end of the molecule. For example, linoleic acid is referred to as an n-6 fatty acid.



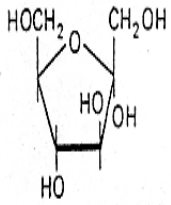
PUF 20 (n-3)



PUF 22 (n-3)



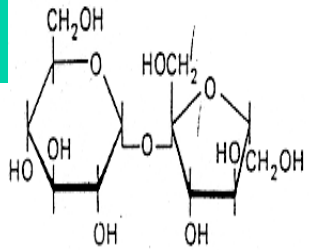
Glucose



Fructose

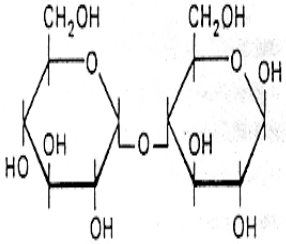
Disaccharides

G — F



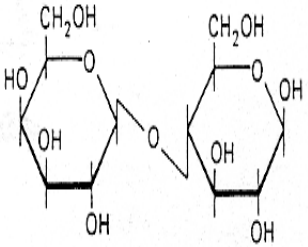
sucrose

G — G



maltose

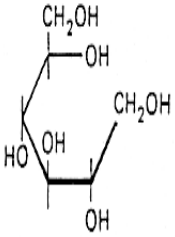
Gal — G



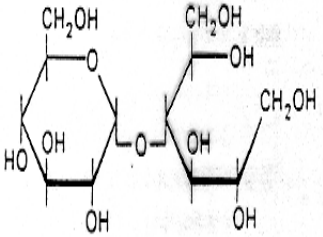
lactose

Modified carbohydrates

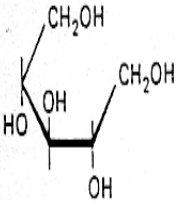
(glucose) (sorbitol)



sorbitol



malitol



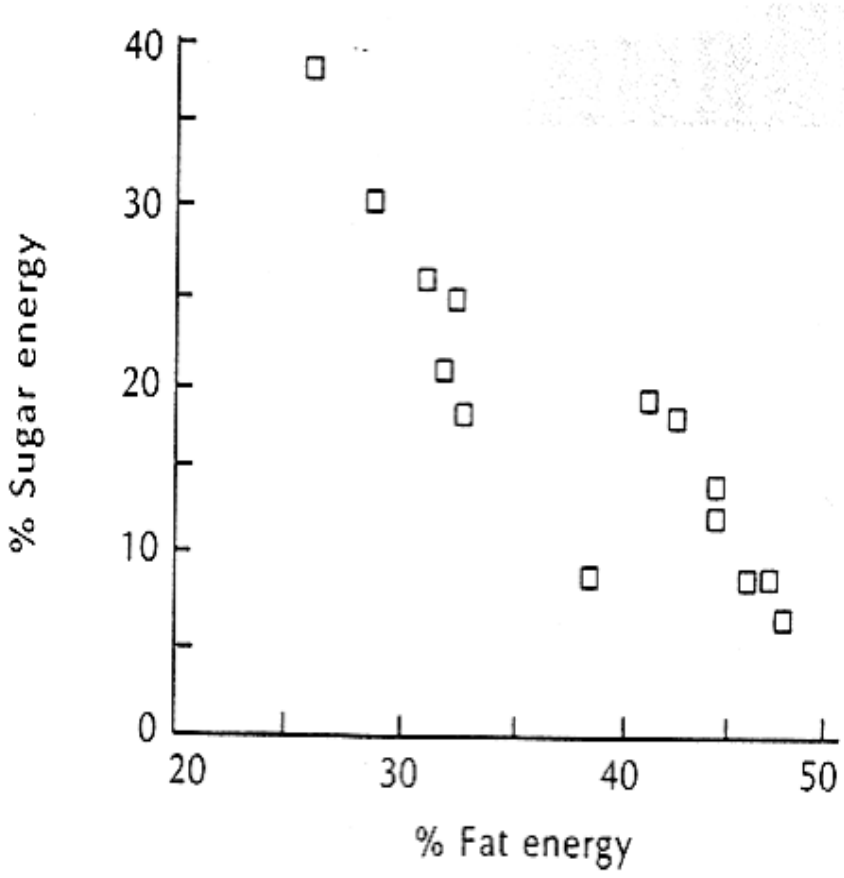
xylitol

Large variety in european sugar consumption

Average daily intakes of total sugars in six countries of the European Union

Country	g/day	% energy
1995		
The Netherlands	131	21.2
United Kingdom	100	18.4
Belgium	96	15.2
Ireland	90	14.6
Germany	80	13.9
Spain	51	8.0

Inverse relationship between intakes of sugars and fats in different affluent countries

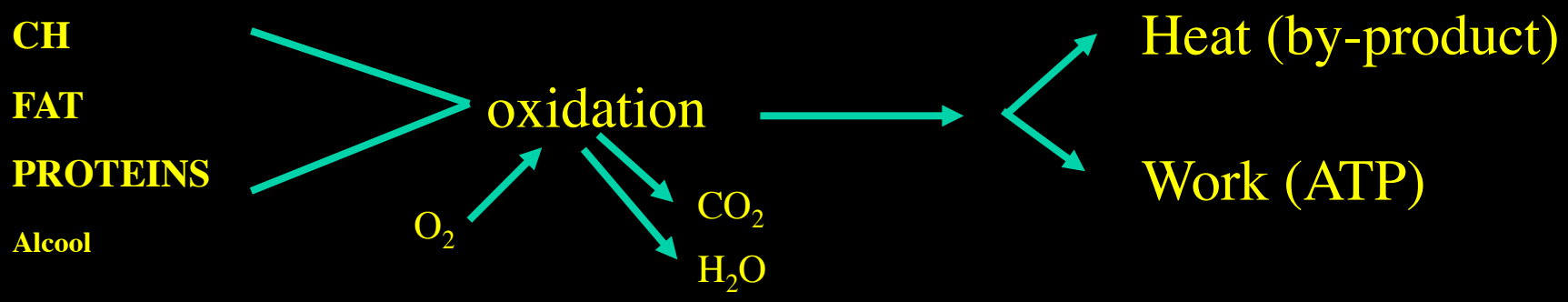


The major fatty acids

Symbol [a]	Common name	Typical fat source
Saturated fatty acids		
2:0	Acetic	Vinegar
4:0	Butyric	Butterfat
8:0	Caprylic	Palm kernel oil
10:0	Capric	Coconut oil
12:0	Lauric	Coconut oil
14:0	Myristic	Butterfat, coconut oil
16:0	Palmitic	Most fats and oils
18:0	Stearic	Most fats and oils
20:0	Arachidic	Lard, peanut oil
22:0	Behenic	"Caprenin"
Unsaturated fatty acids		
16:1 n-7	Palmitoleic	Fish oils
18:1 n-9 (cis)	Oleic	Most fats and oils
18:1 n-9 (*trans*)	Elaidic	Hydrogenated vegetable oils, butterfat, beef fat
18:2 n-6	Linoleic acid	Most vegetable oils
18:3 n-3	α-Linolenic	Soybean, canola oils
20:1 n-11	Gadoleic	Fish oils
20:3 n-9	Eicosatrienoic	Essential fatty acid-deficient animals
20:3 n-6	Dihomo-gamma-linolenic	
20:4 n-6	Arachidonic	Lard
20:5 n-3	Eicosapentaenoic	Fish oils
22:1 n-9	Erucic	Rapeseed oil
22:6 n-3	Docosahexaenoic	Fish oils

Energy in Biomolecules

Oxidative reactions : ***adjustment and multi-fuels***



Yield : 25-40 %

1 kcalorie = 4, 184 Joule

Needs / day : 1800-3600 kcal / jour (2200-2800 kcal)

100 g of chips : 500 kcal

100 g of yoghurt : 62 kcal (= spent after 30 min of walking)

CH : 4 kcal/g

FAT : 9 kcal/g

PROTEIN : 4 kcal/g

Alcool : 7 kcal/g

Metabolism and Basal Metabolism (BM)

Metabolism : all biochemical reactions

* catabolism CH/F/P---> oxidation -----> energy

* anabolism CH/F/P ---> syntheses -----> storage

Basal Metabolism

*Quantity of energy spent at rest, awake, starved, and relaxed mentally and physically

- internal work : brain (20 %), heart, ventilation, peristaltic contraction, muscular tone,….

- temperature

* ± 1200-1800 kcal / jour

BM + meal (Resting Metabolic Rate)

± 200 kcal

Factors tha influence the BM: size/height, age, sexe, endocrine activity,…

(kcal/g) :

CH : 4

Lipids : 9

Proteins : 4

Alcool : 7

Expenditures (/ BM)

sleeping : 1

studying : 1.4

walking : 2.5-5

skiing : 15

Current views of sugars and obesity

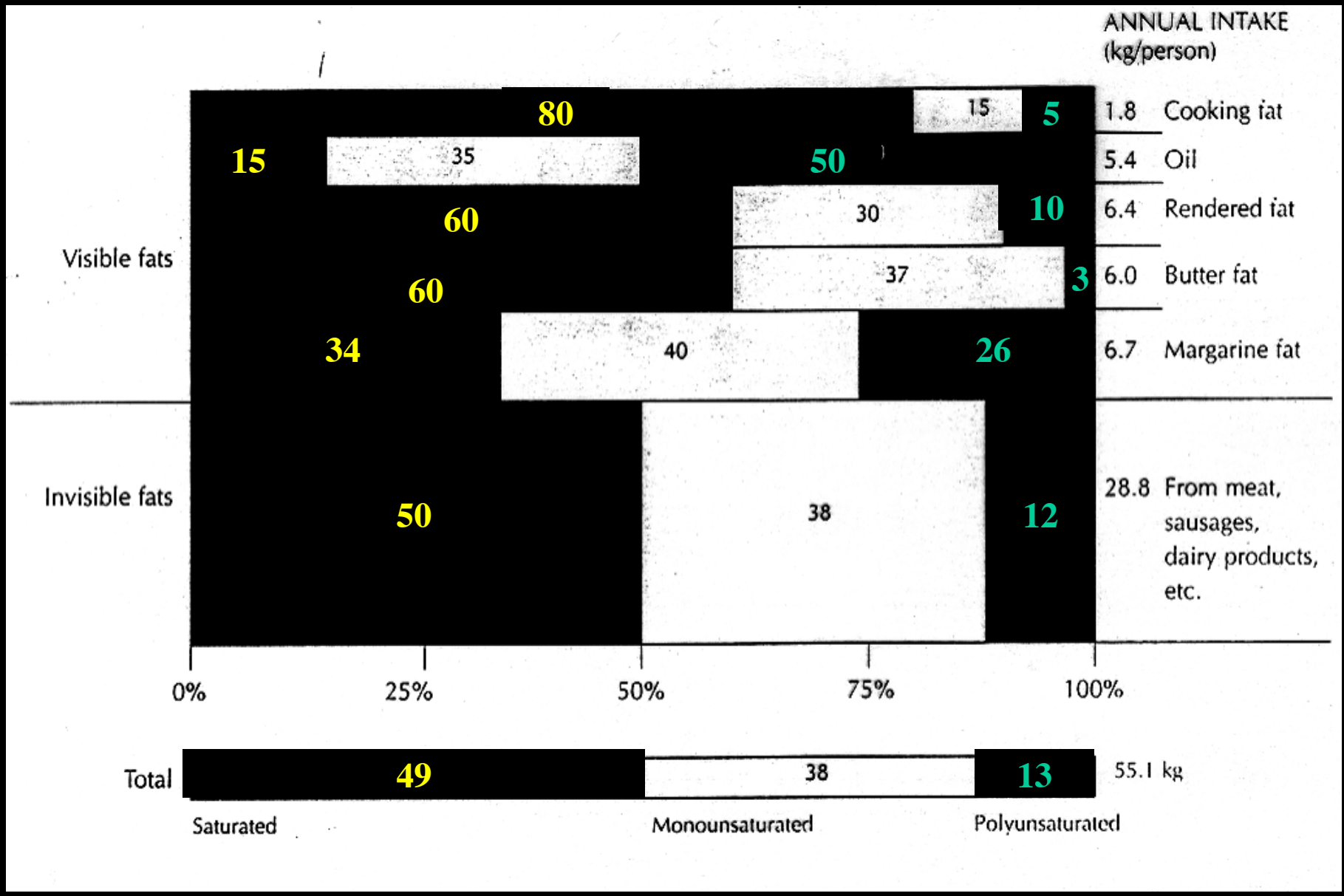
Diets rich in fat are more likely to promote the development of obesity than those rich in carbohydrates

1) **storage of fat is virtually illimited**
2) **human beings have limited ability but still convert excess of CH to fat**
3) **each gram of fat consumed has more than twice as many calories as each gram of CH**
4) **satiety feeling is lower for fat**

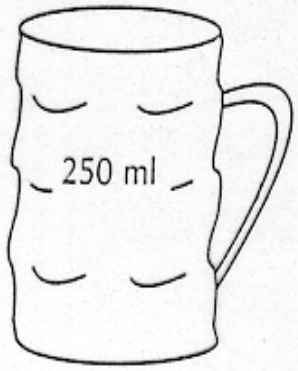
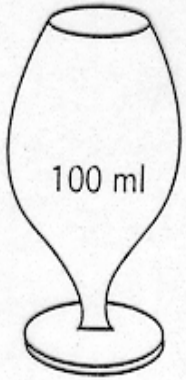
Apports quotidiens des principaux acides gras alimentaires chez des hommes d'âge moyen en Finlande, aux Pays-Bas, aux États-Unis et dans l'île de Corfou, en Grèce.

	Apports d'acides gras (g/jour)			
	Finlande	Pays-Bas	États-Unis	Corfou
Acides gras saturés				
Acide laurique (C12:0)	4	2	2	0,3
Acide myristique (C14:0)	12	8	6	1,1
Acide palmitique (16:0)	38	30	30	16
Acide stéarique (C18:0)	20	15	14	3
Autres saturés*	7	6	4	2
Acides gras mono-insaturés				
Acide oléique (*cis*-C18:1*n*-9)	40	29	37	56
Trans C16:1 + C18:1	5	7	4	0,2
Acides gras poly-insaturés				
Acide linoléique (C18:2*n*-6)	8	12	17	13
Acide α-linolénique (C18:3*n*-3)	2	2	2	1
Acide eicosapentaénoïque (C20:5*n*-3)	0,4	0,3	0,1	0,2
Acide docosahexaénoïque (C22:6*n*-3)	0,3	0,1	0,1	0,6

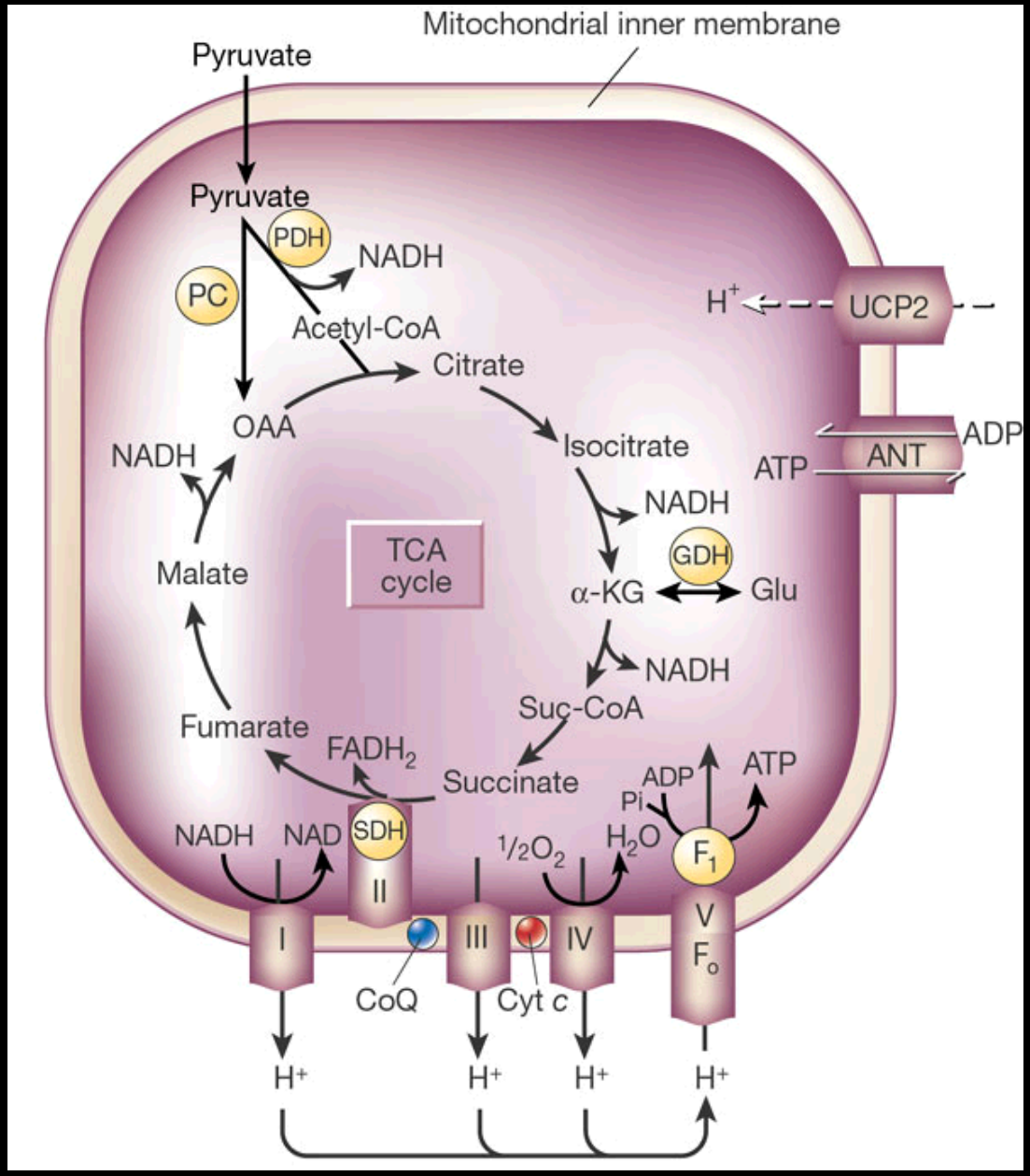
Total individual fat intake (± 55 Kg/year =150 g/day 39 % of energy intake) -Germany-



Alcohol as a source of energy

Beer	Wine	Fortified wine	Spirits eau de vie
			
3.5–5.5% volume alcohol 6.9–10.9 g	11–13% volume alcohol 8.7–10.3 g	17–22% volume alcohol 8.1–10.4 g	40% volume alcohol 7.6 g

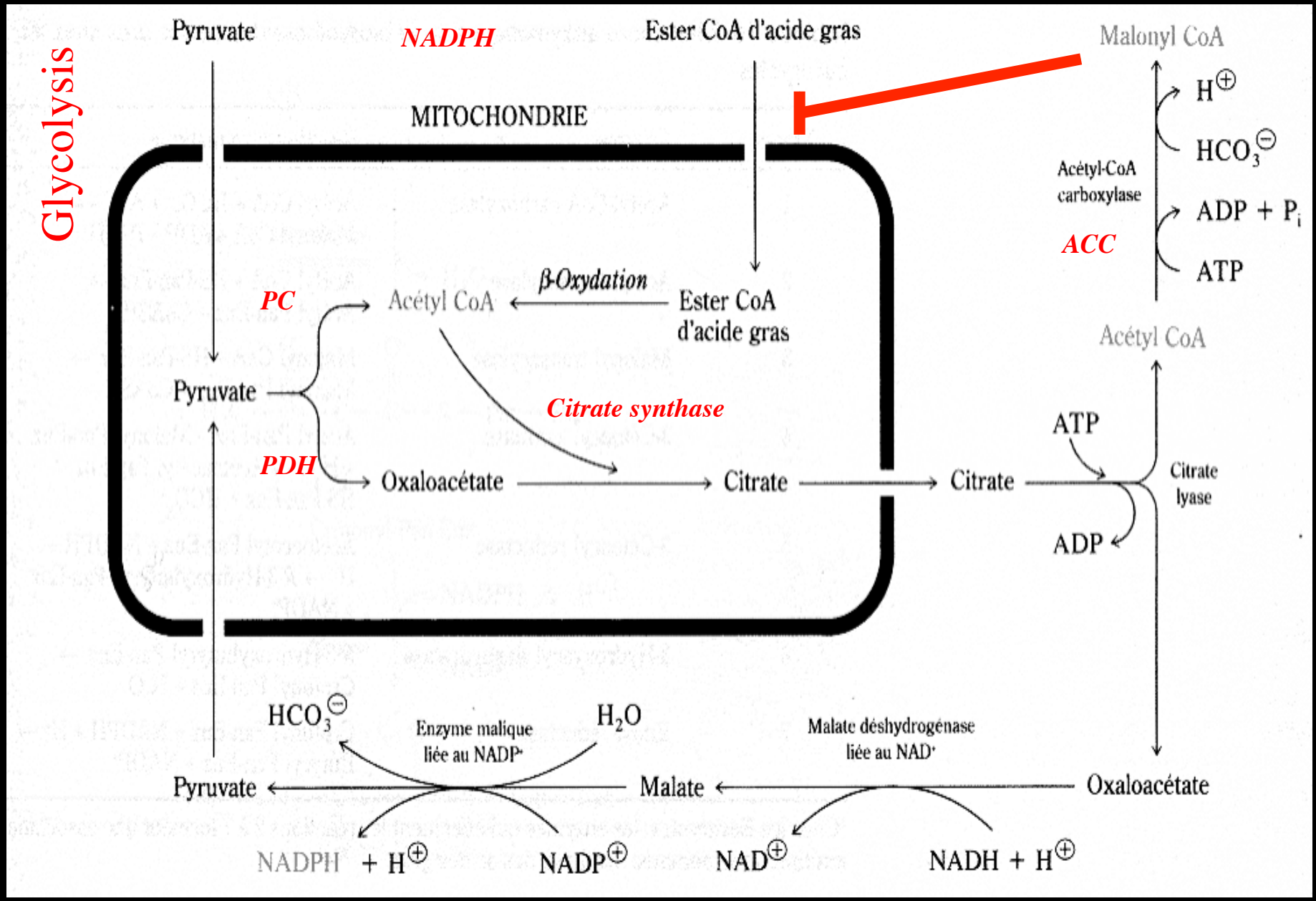
The TCA cycle and respiratory chain in a mitochondria



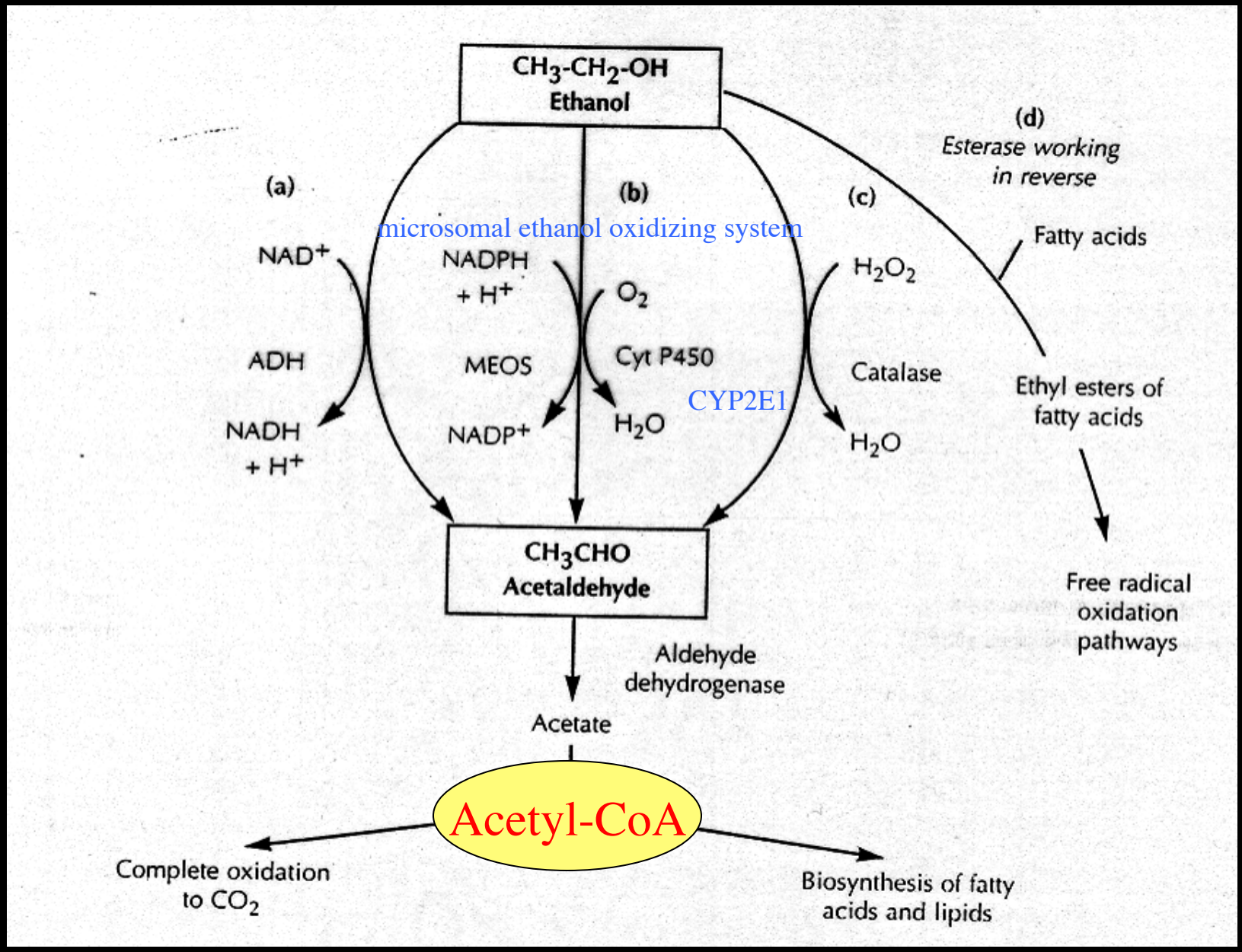
Substrate oxidation in the TCA cycle activates the respiratory chain leading to the generation of ATP which is subsequently translocated to the cytosol.

ANT, adenine nucleotide translocator; GDH,glutamate dehydrogenase;
Glu, glutamate;
KG, ketoglutarate;
OAA, oxaloacetate;
PC, pyruvate carboxylase;
PDH, pyruvate dehydrogenase;
Suc-CoA, succinyl-CoA;
SDH, succinate dehydrogenase;
TCA, tricarboxylic acid;
UCP2, uncoupling protein 2.

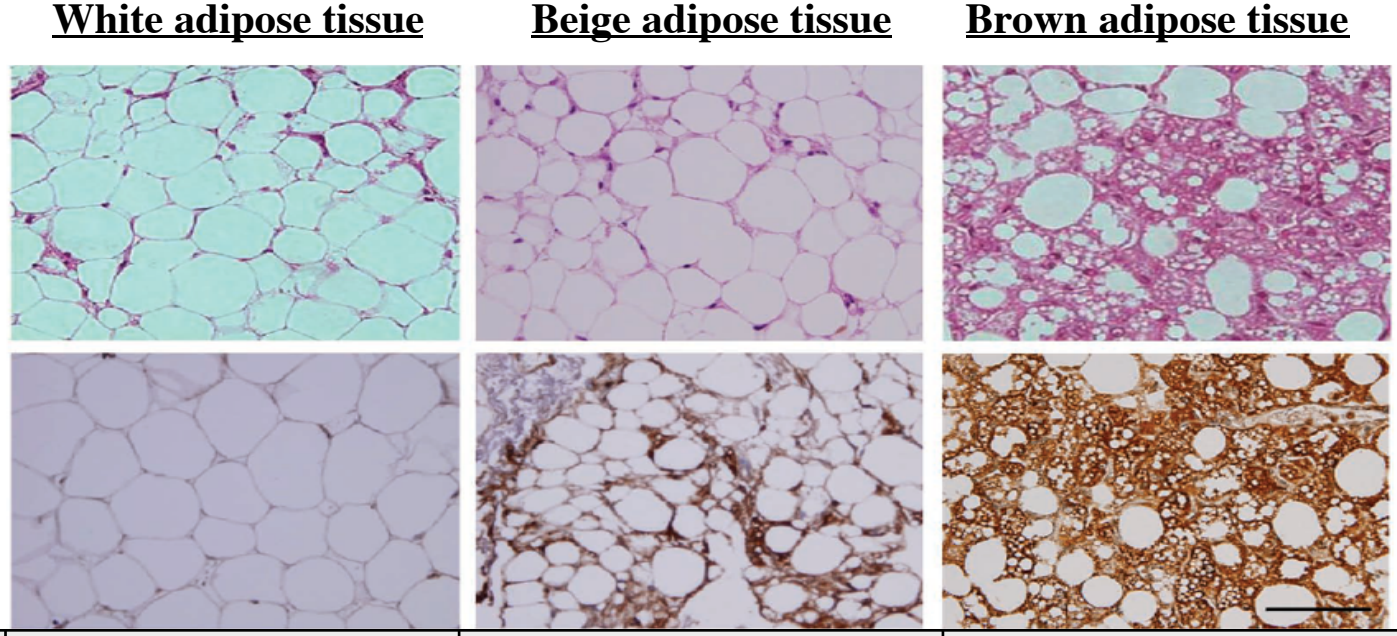
Formation of Acetyl-CoA, Malonyl-CoA and NADPH = precurosrs for lipid synthesis



Alcohol as an energetic fuel ?



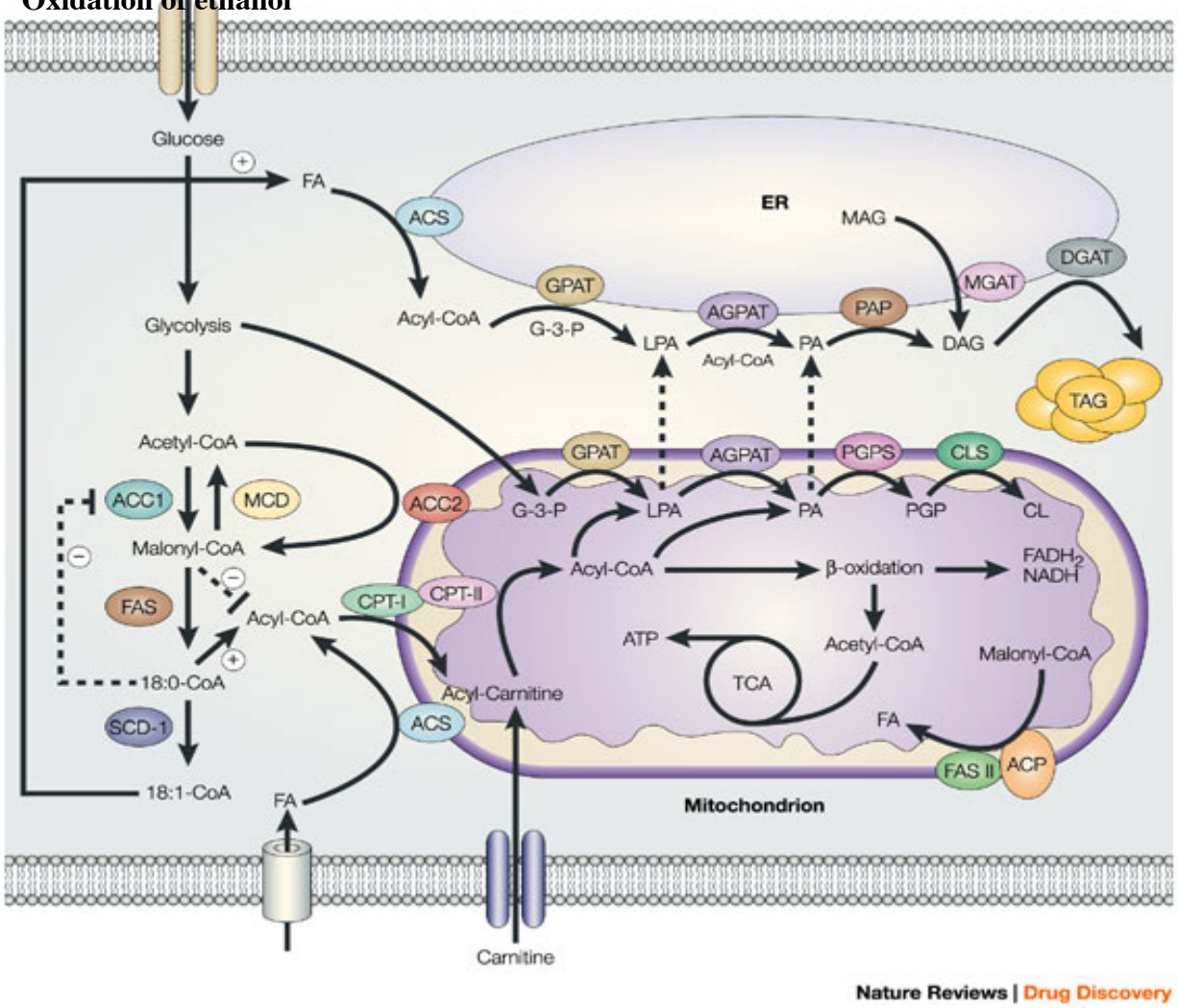
The adipose tissues : characteristics and functions



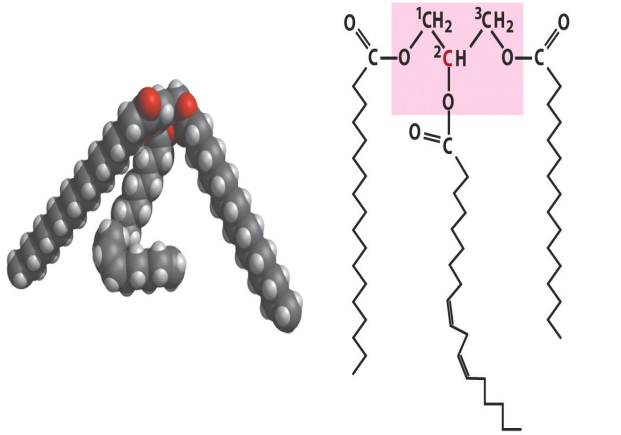
Mitochondrial content	Low	High	High
Lipid droplets	One unilocular	Numerous	Numerous
UCP-1 expression	None or very low	High	High
Thermogenic ?	No	Yes	Yes
Lipogenesis ?	High	High	High
Lipolysis	Moderate	High	High

Acetyl-CoA : a metabolic node with multiple functions and enzymatic pathways for TAG synthesis

Oxidation of glucose excess
β-oxidation of excess FA
Oxidation of ketogenic amino acid
Oxidation of ethanol



TAG : 0.5 et 2 mmol/L
or 0.45 et 1.75 g/L



1-Stearoyl, 2-linoleoyl, 3-palmitoyl glycerol, a mixed triacylglycerol

RDCI : 30 % (DCI : 40 % or more)

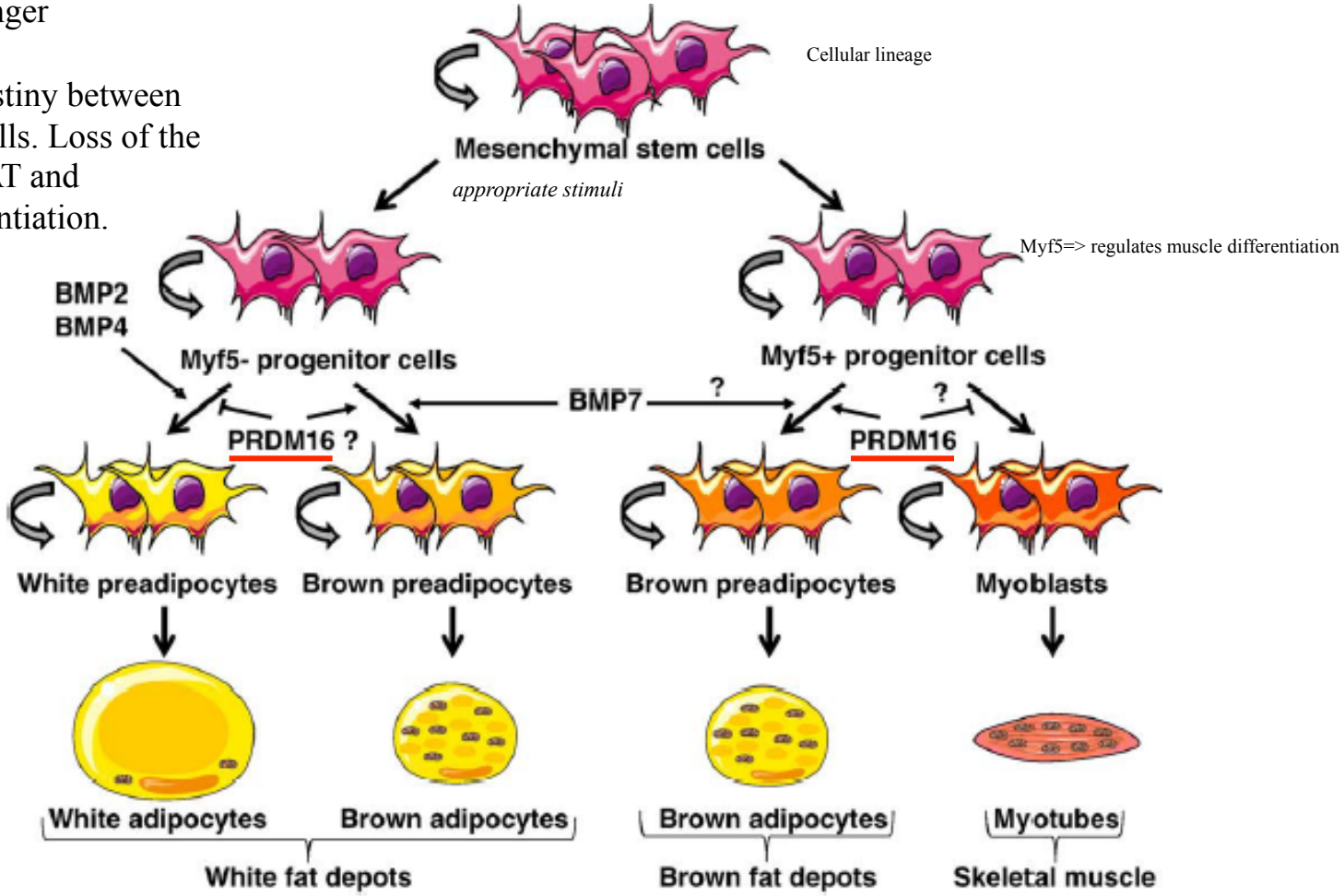
1 g of TG : 9 kCal

(± 2200 kcal/day)

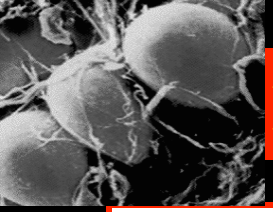
The origin of fat cells in different fat depots

PRDM16 controls the differentiation of brown adipocytes. The protein encoded by this gene is a zinc finger transcription factor.
Controls the cell fate/destiny between muscle and brown fat cells. Loss of the gene causes a loss of BAT and promotes muscle differentiation.

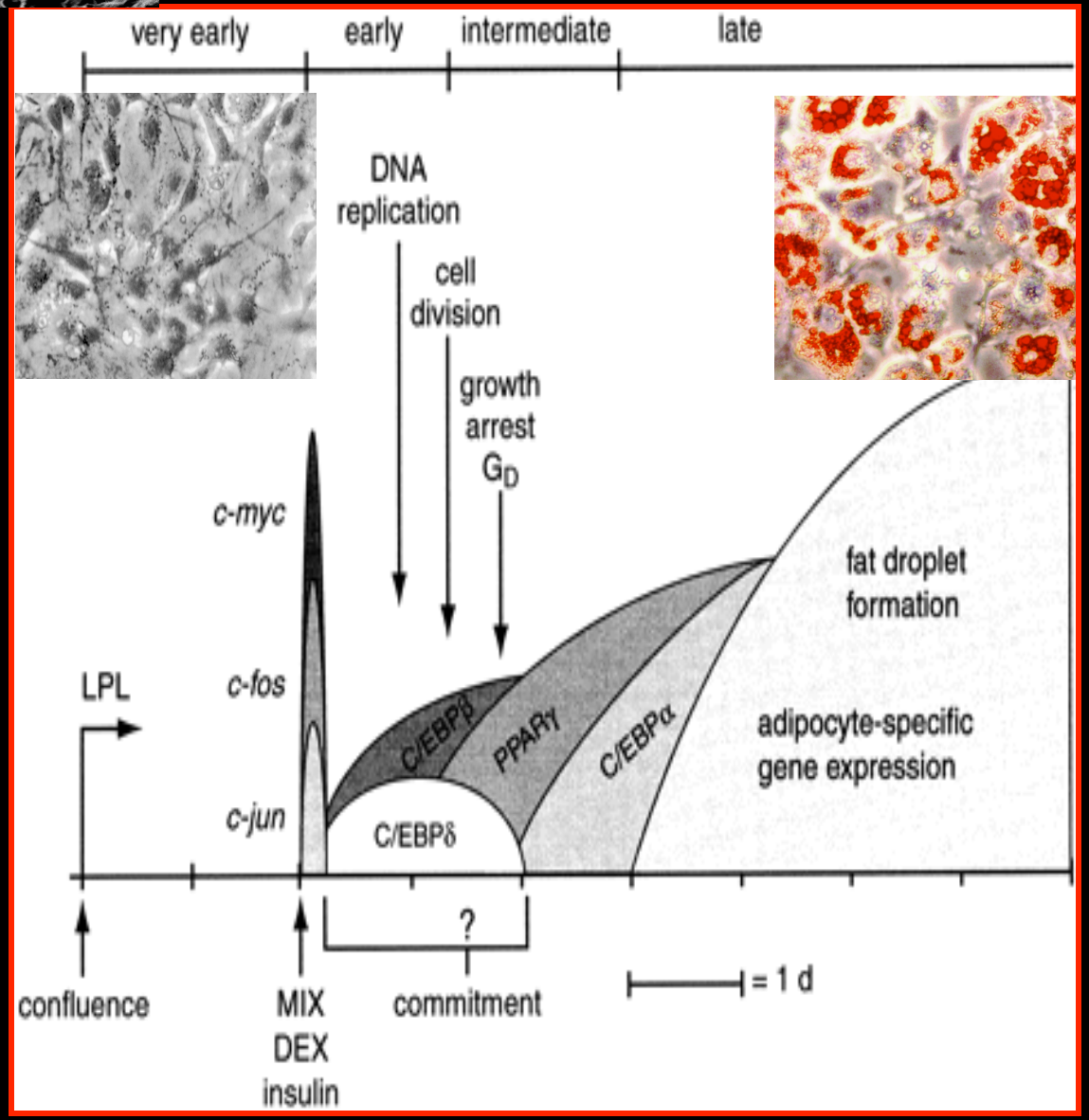
Differentiation step



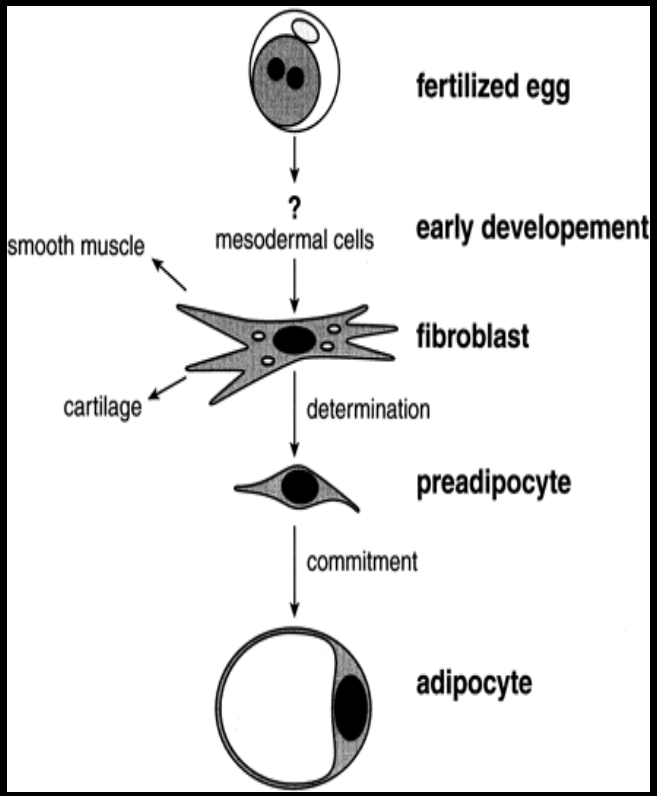
PR-(PRD1-BF-RIZ1 homologous) domain protein 16=>PRDM16, the key factor in the differentiation of brown fat cells



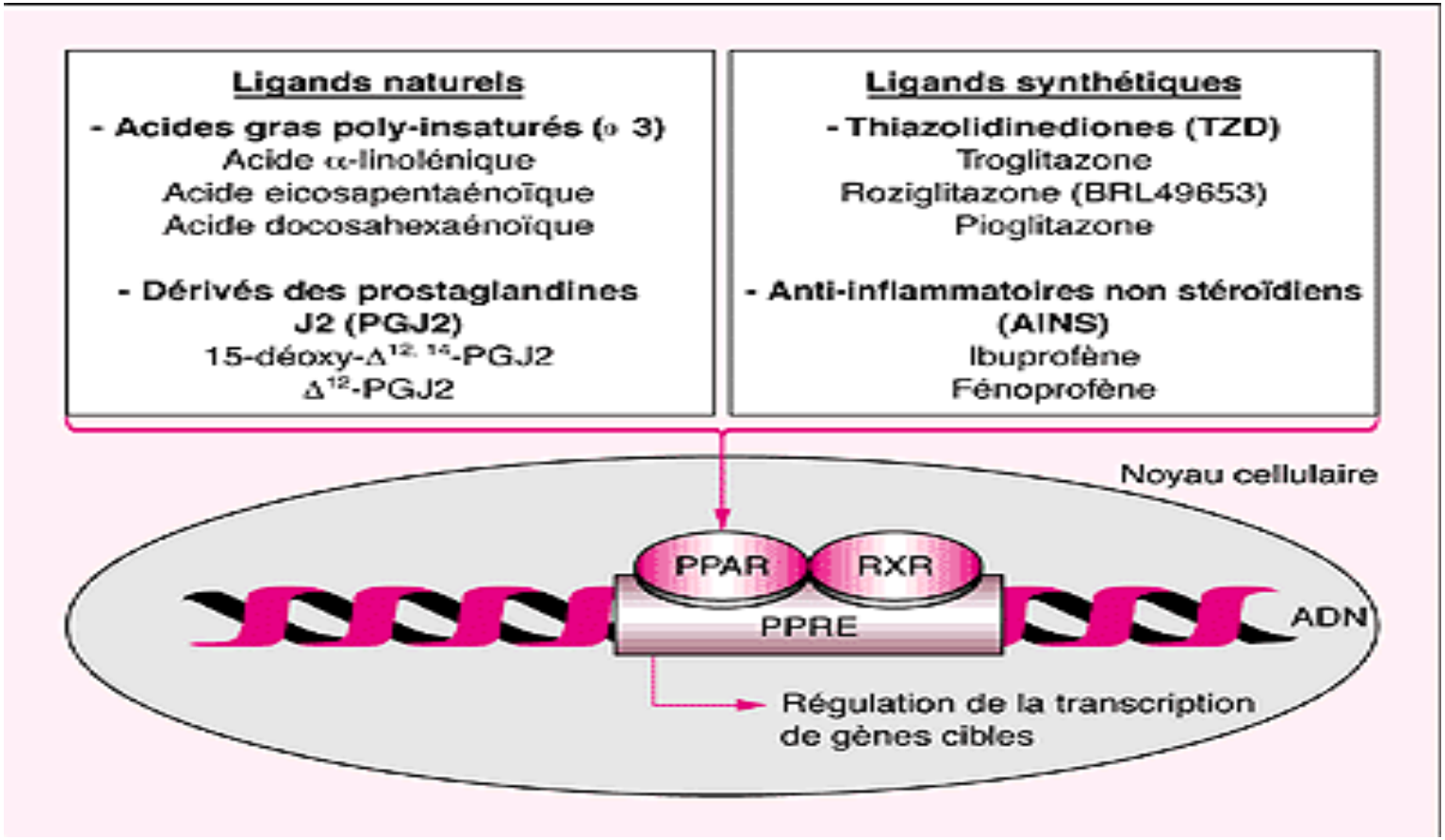
Progression of 3T3-L1 preadipocyte differentiation



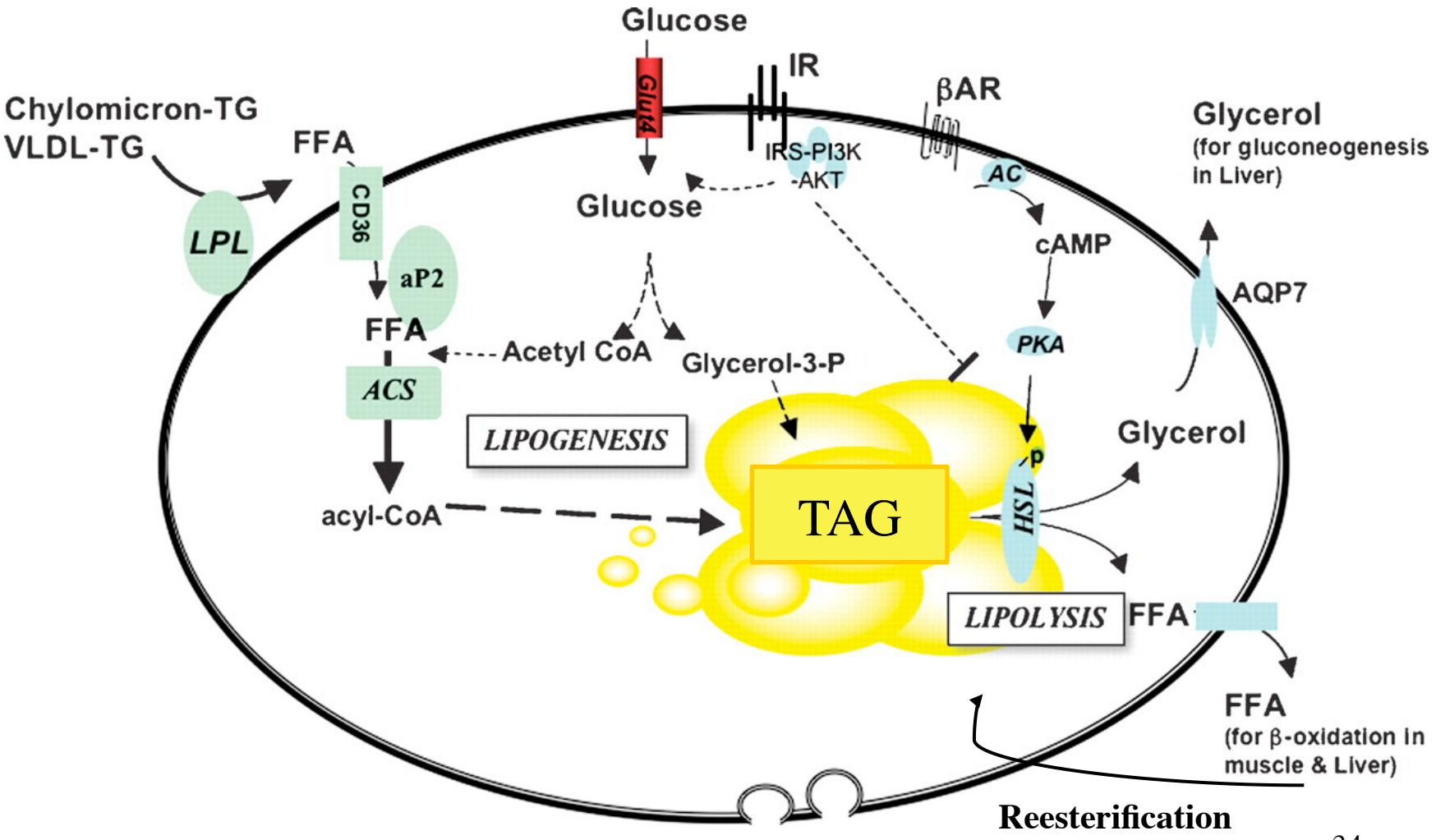
LPL, lipoprotein lipase;
C/EBPs, CCAAT/enhancer binding proteins
PPAR, peroxisome proliferator-activated receptor
MIX, methylisobutylxanthine
DEX, dexamethasone.



PPARγ ligands : natural or synthetic

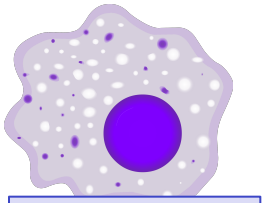


Adipocyte TAG content is the result of a balance between lipolysis and lipogenesis



Sethi, 2007, J Lipid Res.

Adipose tissues also play an important endocrine role



Immune system

Induction of a pro-inflammatory response / state

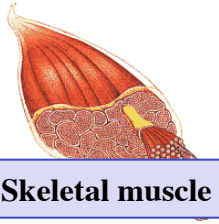
IL-6 / TNFα / TSP-1

Macrophage chemoattraction

MCP-1

increases FFA uptake and oxidation in muscle (CD36 FFA-Transporter)
represses PEPCK in liver (a gluconeogenic enzyme)

Increases insulin sensitivity

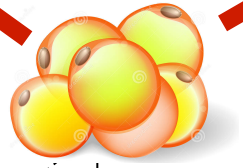


Skeletal muscle

Adiponectin

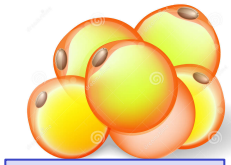
Resistin

Inhibition of insulin-dependent glucose uptake



Chemerin

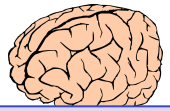
Stimulates adipogenesis and lipolysis



Adipose tissues

Leptin

Favors satiety



Central nervous sytem

PAI-1

Inhibition of fibrinolysis

AGT

Induces vasoconstriction

Apelin

Stimulates angiogenesis

Blood vessels

Insulin : a key factor

Functions (anabolic hormone)

Carbohydrate metabolism

Increase uptake of glucose

* **glycogen synthesis**
* **inhibition of neoglucogenesis**

Fat metabolism

Increase fat storage in adipose tissue

* **stimulates FA synthesis (glucose)**
* **inhibition of TAG hydrolysis**
* **inhibition of FA β-oxidation**

Protein metabolism

Increase protein synthesis

* **promote the use of aa**
* **inhibits protein degradation**

Hormone secretion

* **inhibition of glucagon secretion (α-pancreatic cells)**

Modulators of the release

Stimulation

Blood glucose [ ]
Intestinal glucose [ ]

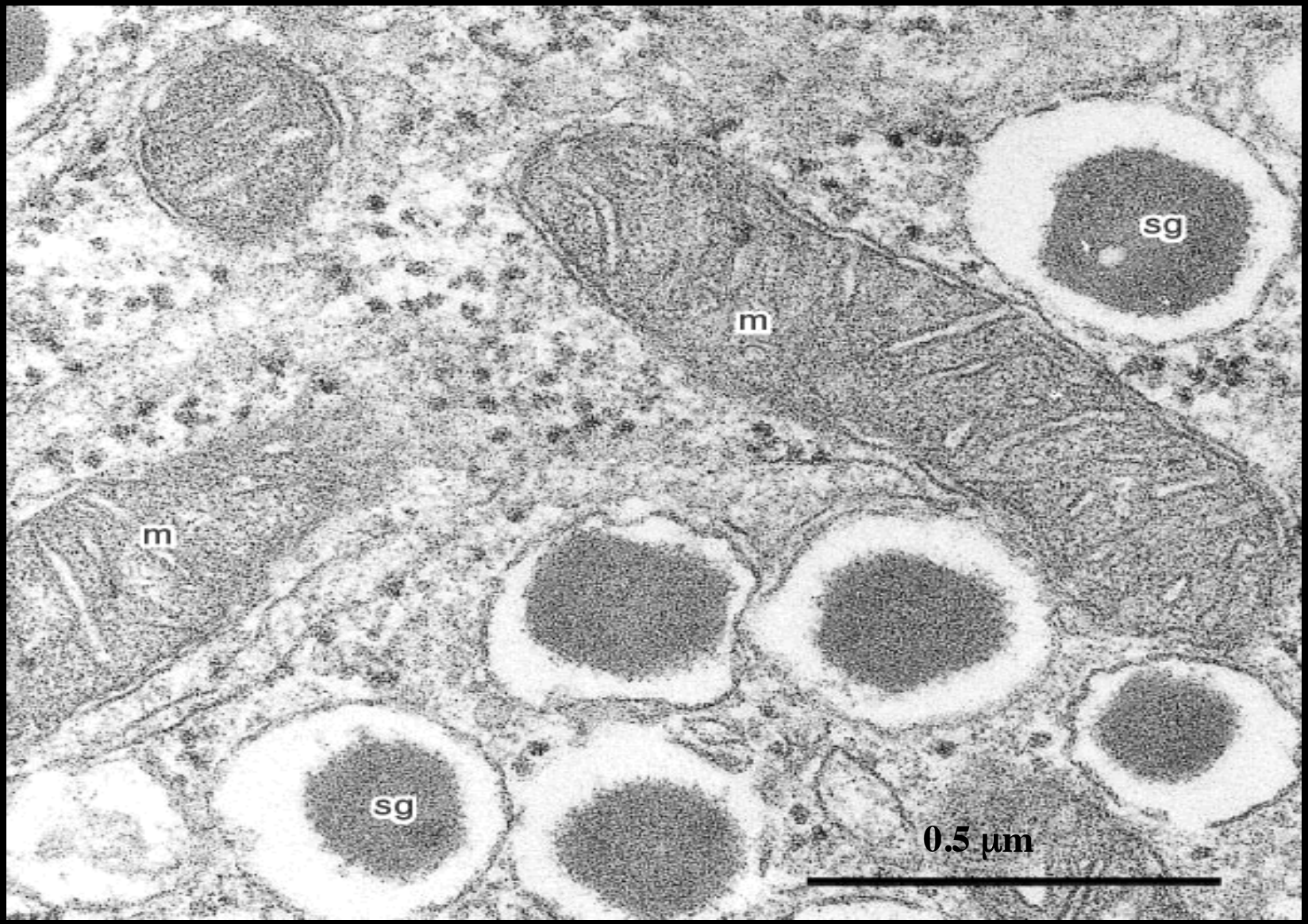
Glucagon level

Inhibition

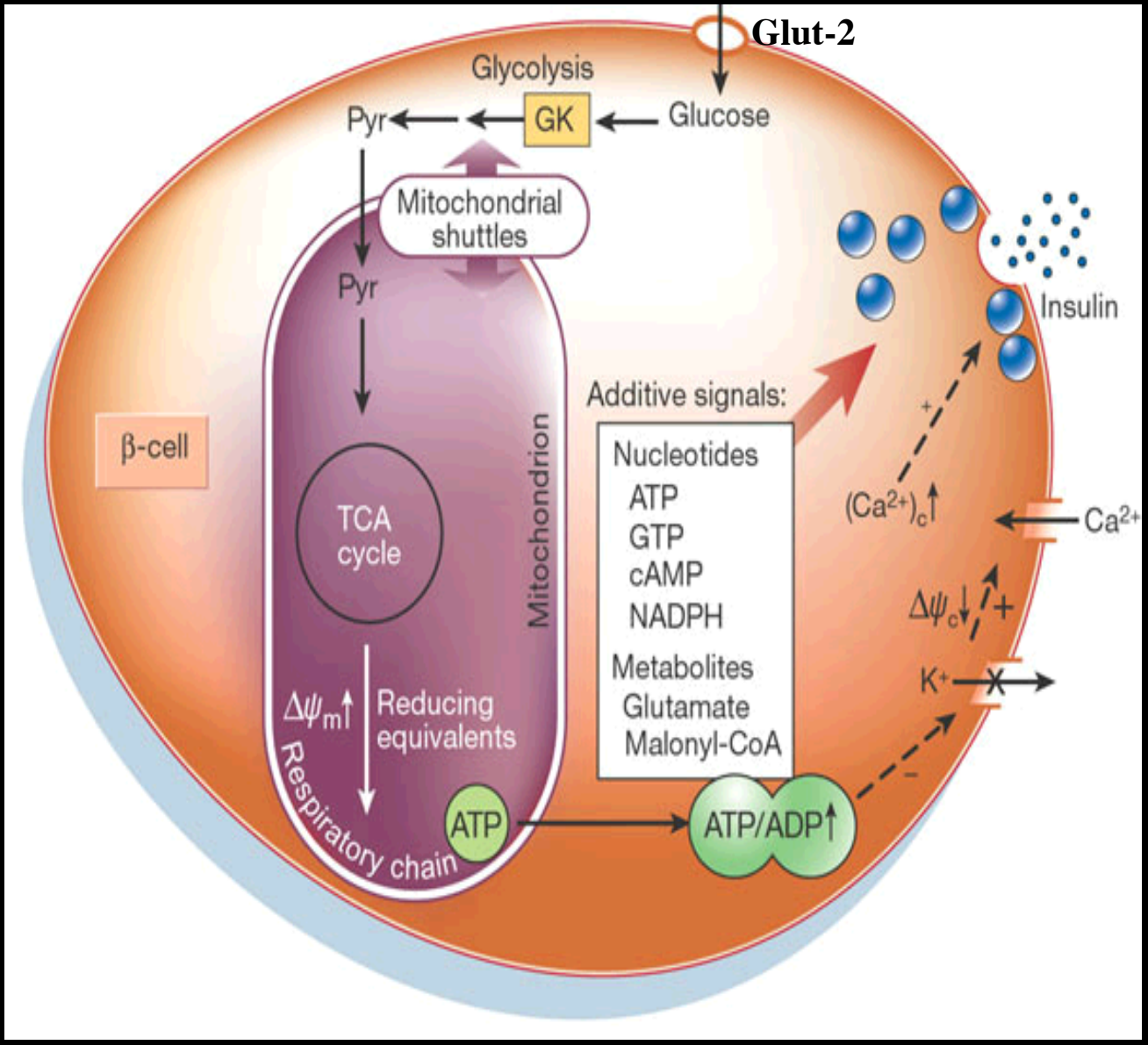
Adrenaline

Somatostatin

Electron micrograph of part of a rat β-cell showing mitochondria (m) and insulin-containing secretory granules (sg).



Model for coupling of glucose metabolism to insulin secretion in the β-cell



Glucose is phosphorylated by glucokinase (GK) and converted to pyruvate (Pyr) Pyruvate enters the mitochondria and fuels the TCA cycle, resulting in the transfer of reducing equivalents to the respiratory chain, leading to hyperpolarization of the mitochondrial membrane and generation of ATP. Subsequently, closure of K_{ATP}-channels depolarizes the cell membrane.
This opens voltage-gated Ca^{2+} channels (VGCC), raising the cytosolic Ca^{2+} concentration ($[Ca^{2+}]c$), which triggers insulin exocytosis.

Type II diabetes

Hyperinsulinemia / Hyperglycemia = insulin resistance

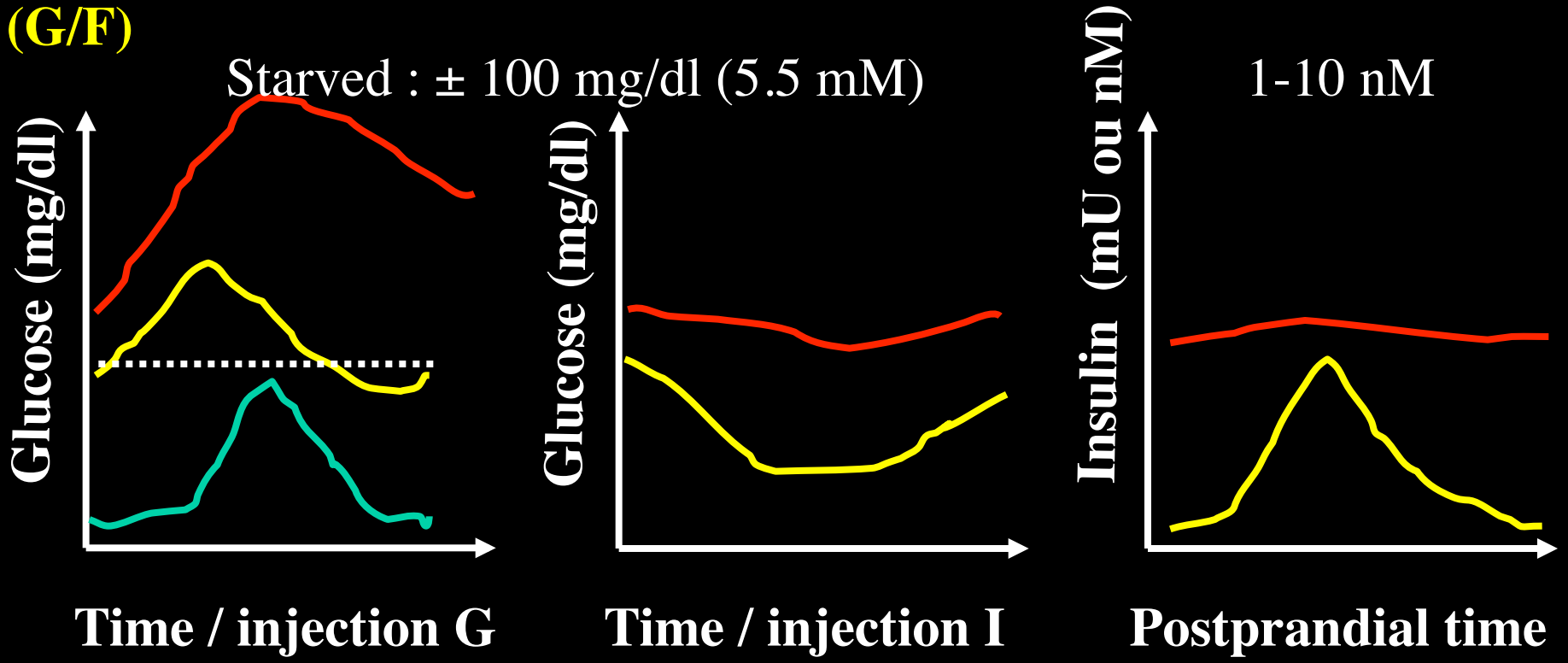
Glucose tolerance
Glycemic index
(G/F)

Insulin sensitivity

Insulin [ ]

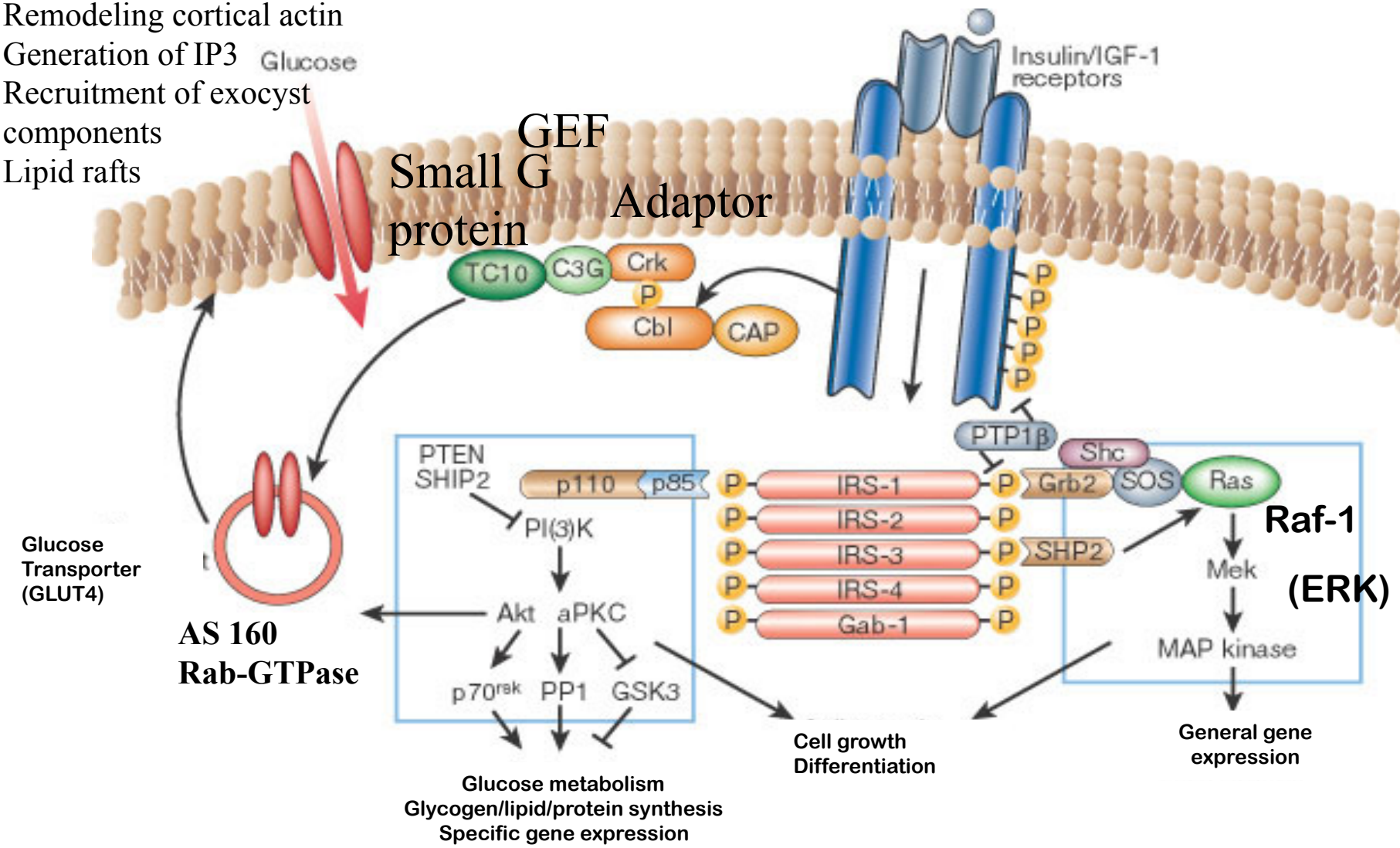
Starved : ± 100 mg/dl (5.5 mM)

1-10 nM



Insulin Signaling Pathway

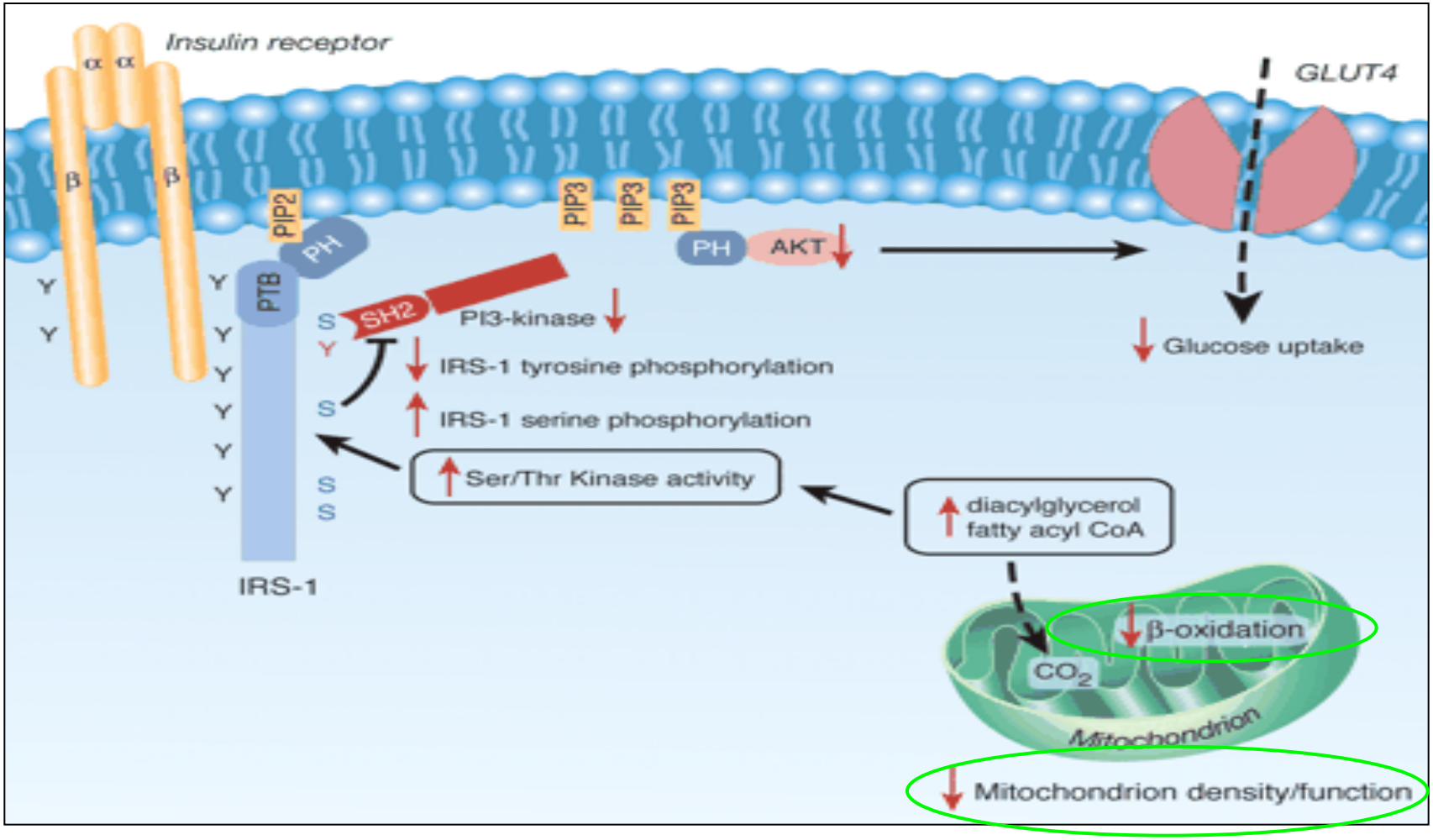
Remodeling cortical actin
Generation of IP3
Recruitment of exocyst components
Lipid rafts



(Saltiel and Kahn, 2001)

Mitochondria dysfunction and Insulin Resistance

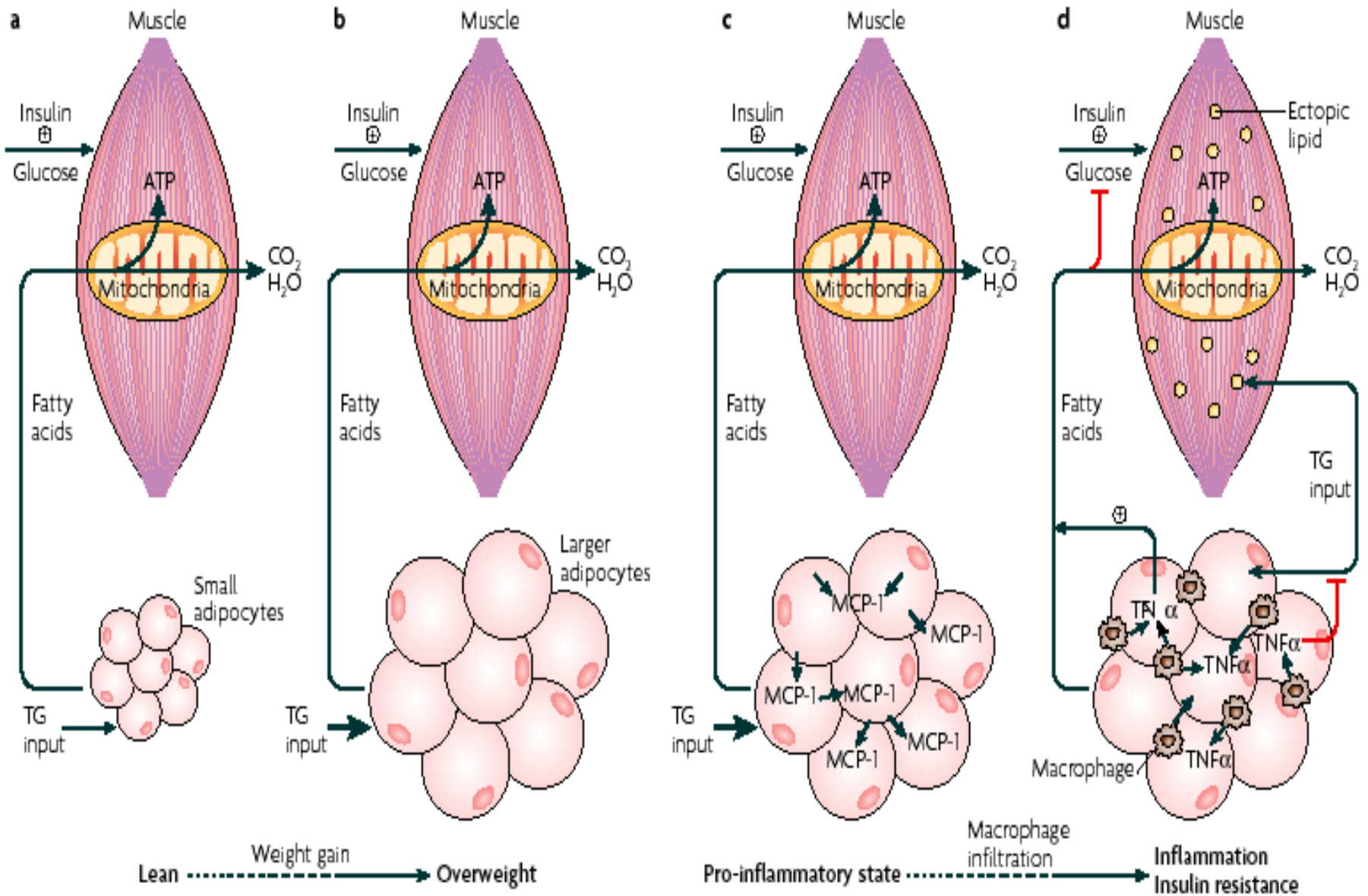
Muscle cells



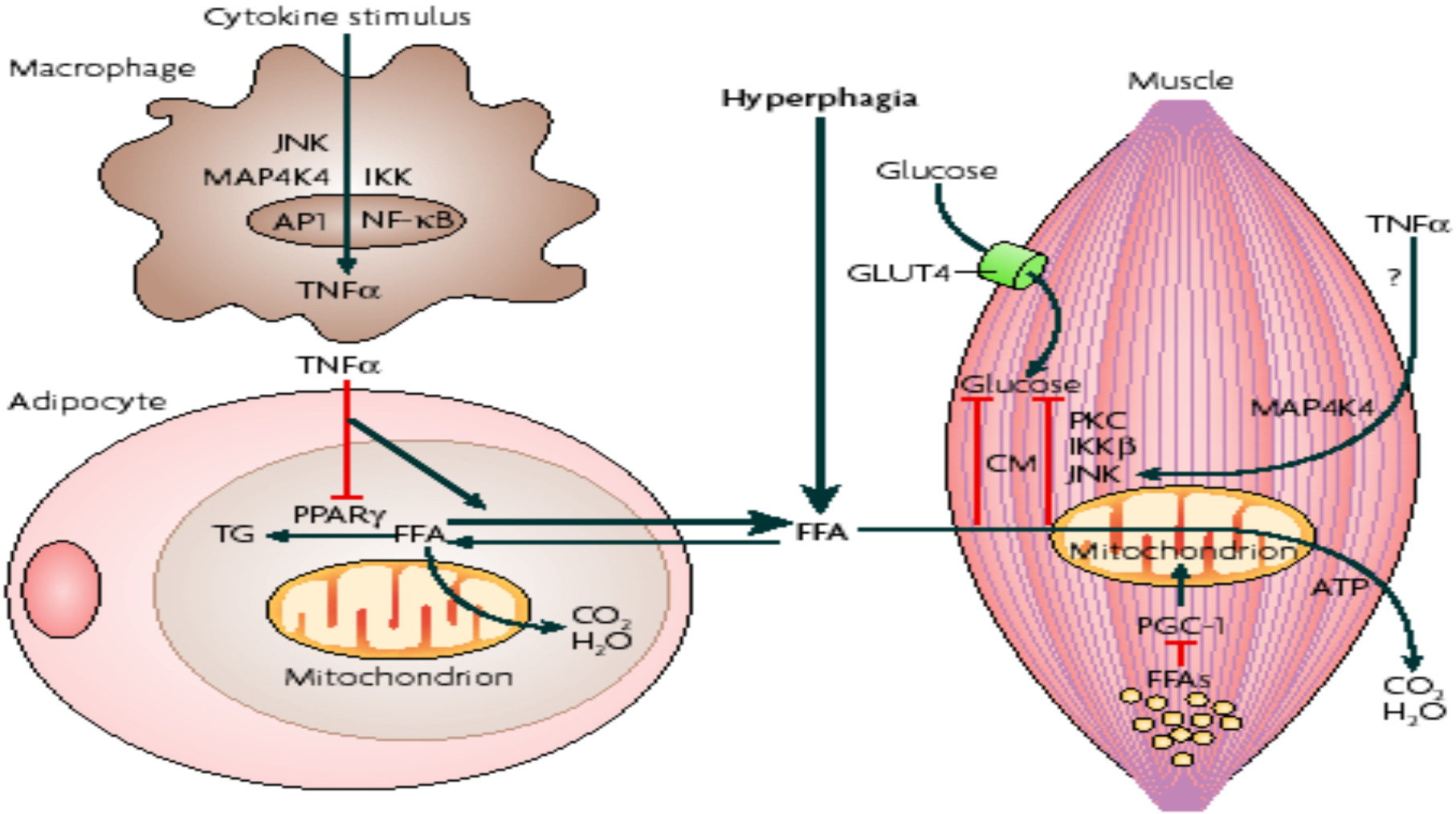
Nature Medicine/Vol 12/Number 1/January 2006

Chronic Inflammation in WAT and Insulin Resistance

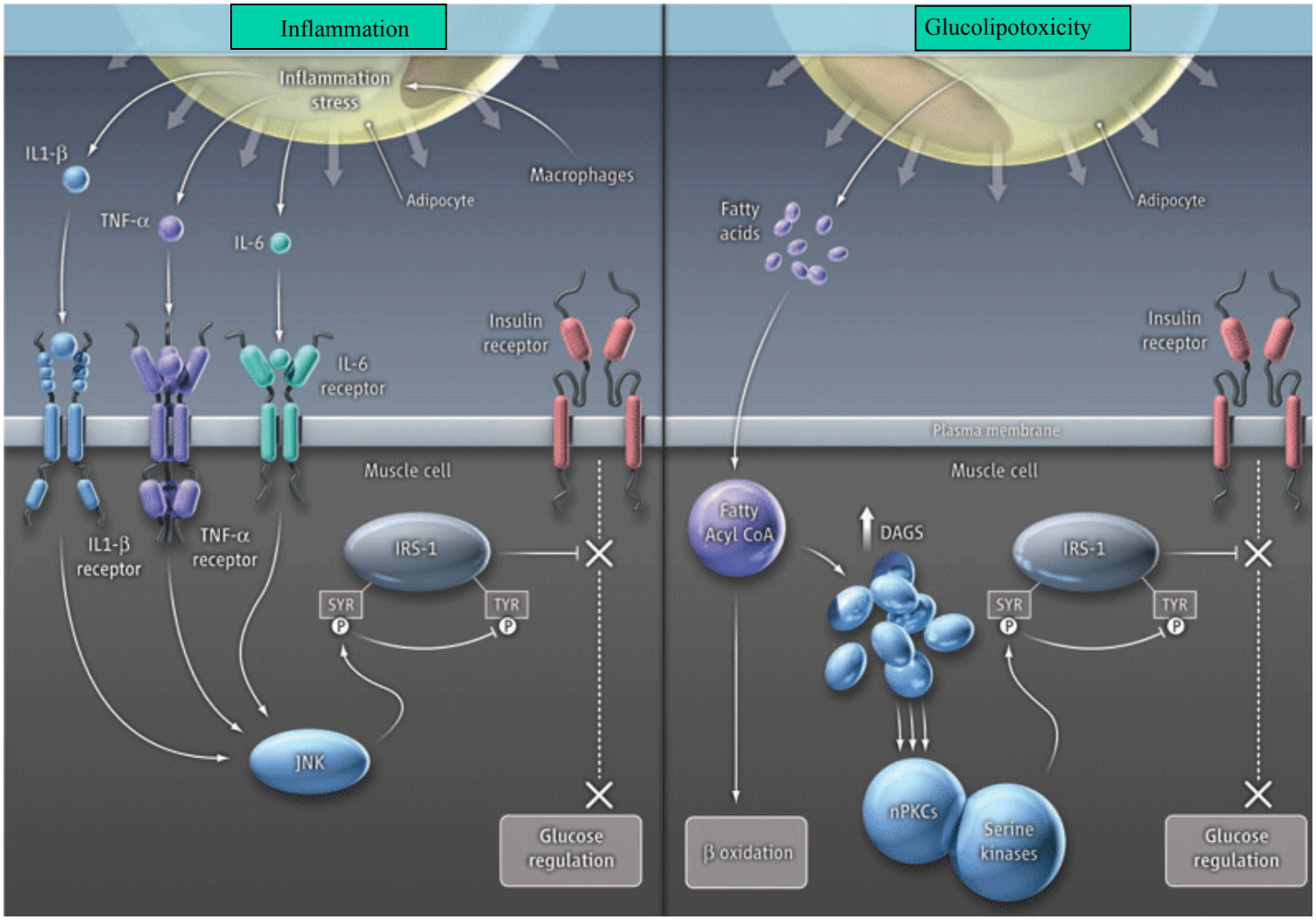
Guilherme-A et al., Nat Rev Mol Cell Biol. 2008;9(5):367-77



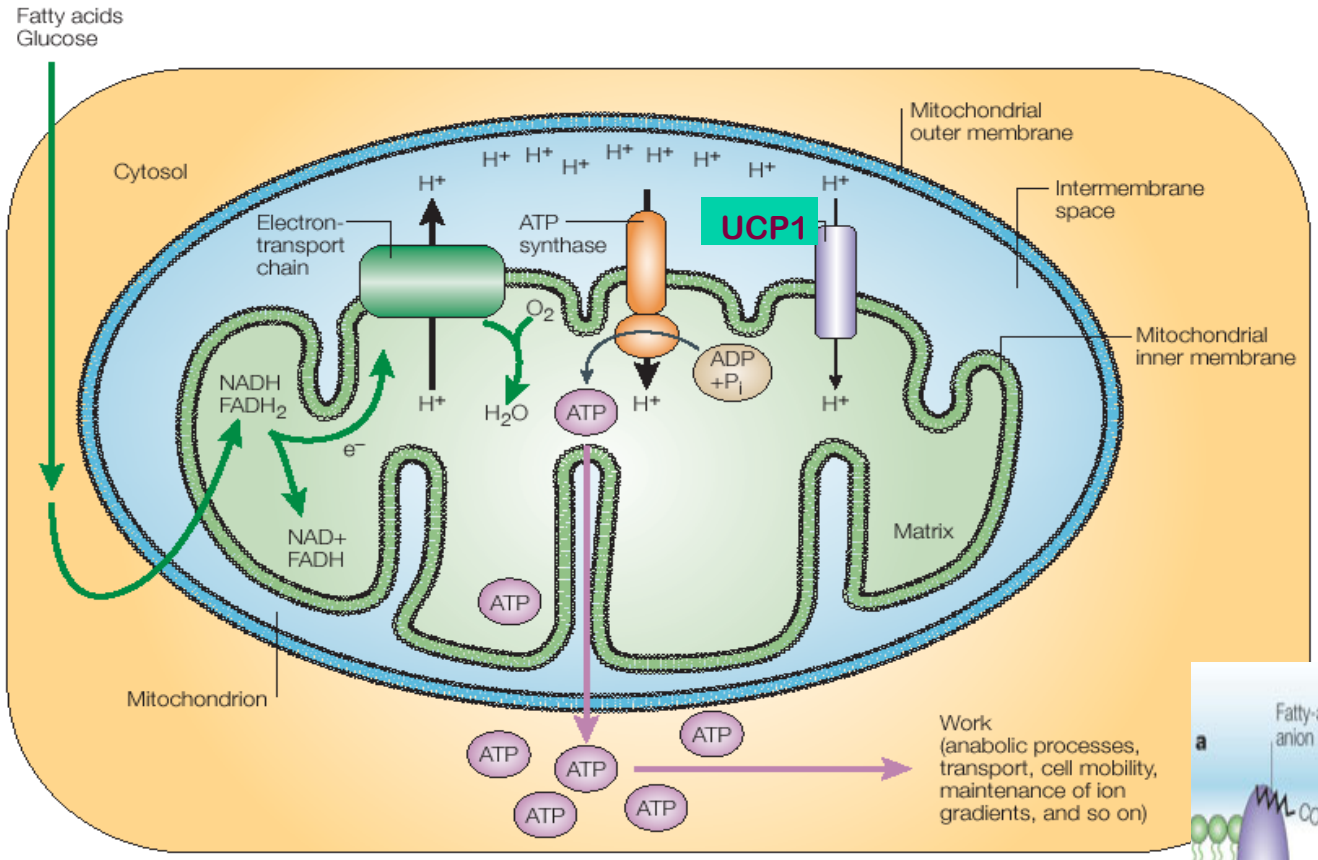
Inflammation blocks TG accumulation in WAT

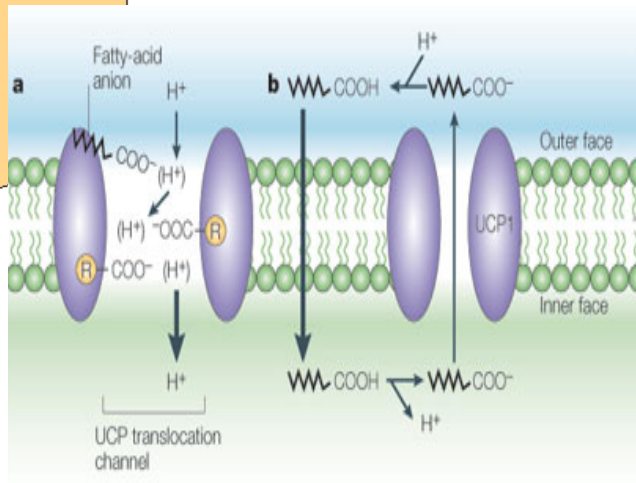


Two hypothesis to explain the mechanisms liking obesity and insulin resistance



Mitochondrial Uncoupling of OXPHOS

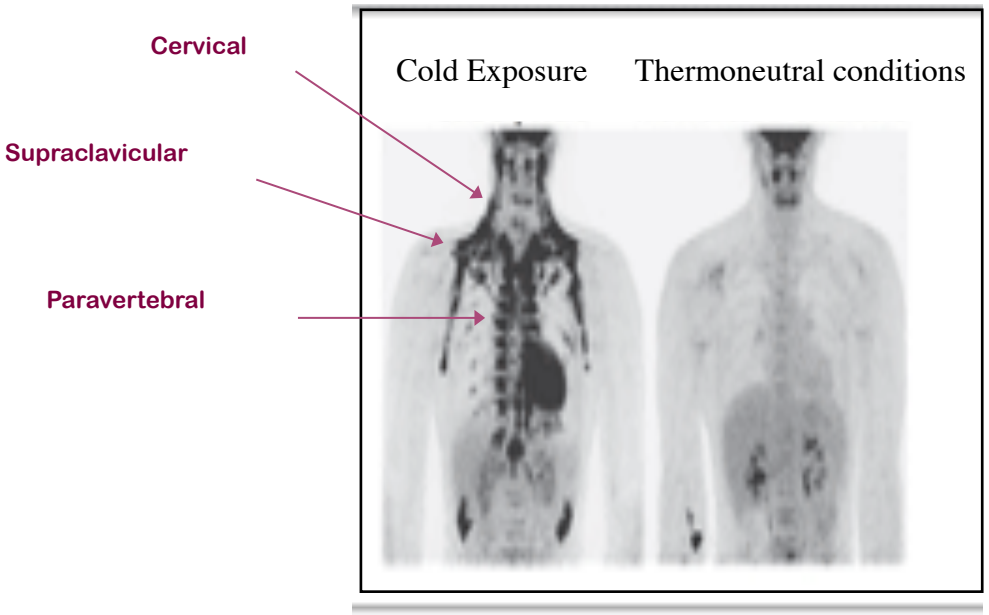




(Krauss et al., *Nature* 2005)

Non-Shivering Adaptative Thermogenesis
Activity of BAT in Human Adults

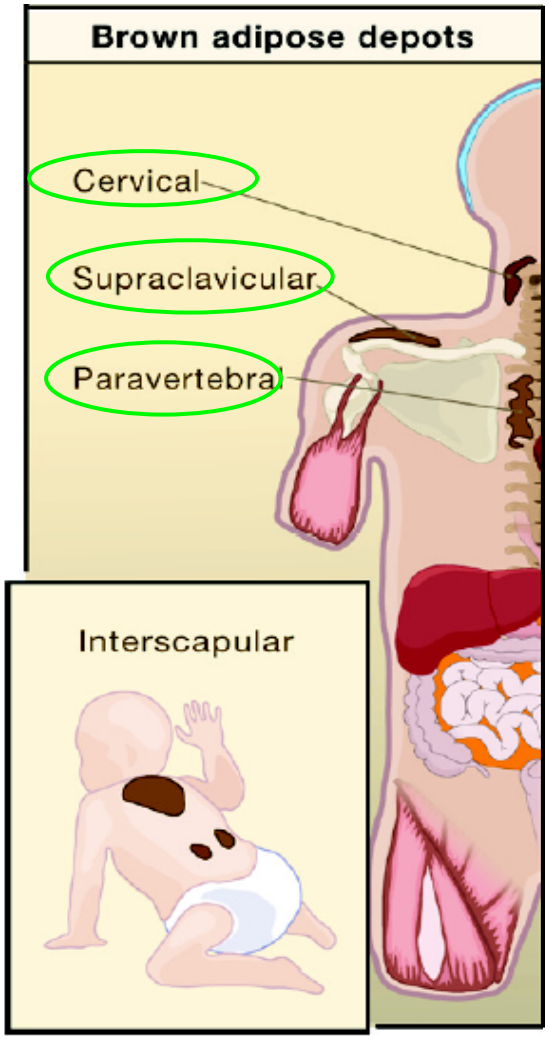
Lean subject with high BAT activity



^{18}Fluorodexyglucose- PEC/CT (computarized tomography)

↓

UCP1

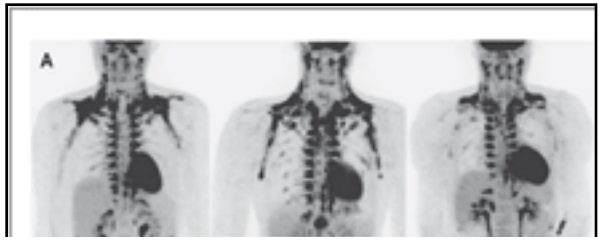


Nederegaard et al., 2007 Am.J. Physiol Endocrinol. Metab.
Van Marken Lichtenbelt et al, 2009 N.Engl. Med
Cypess et al, 2009 N.Engl. Med

Non-Shivering Adaptative Thermogenesis
Activity of BAT in Human Adults

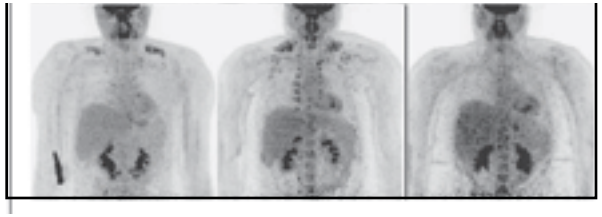
Brown adipose-Tissue activity is negatively correlated with percentage of body fat

Lean subject
with high BAT activity



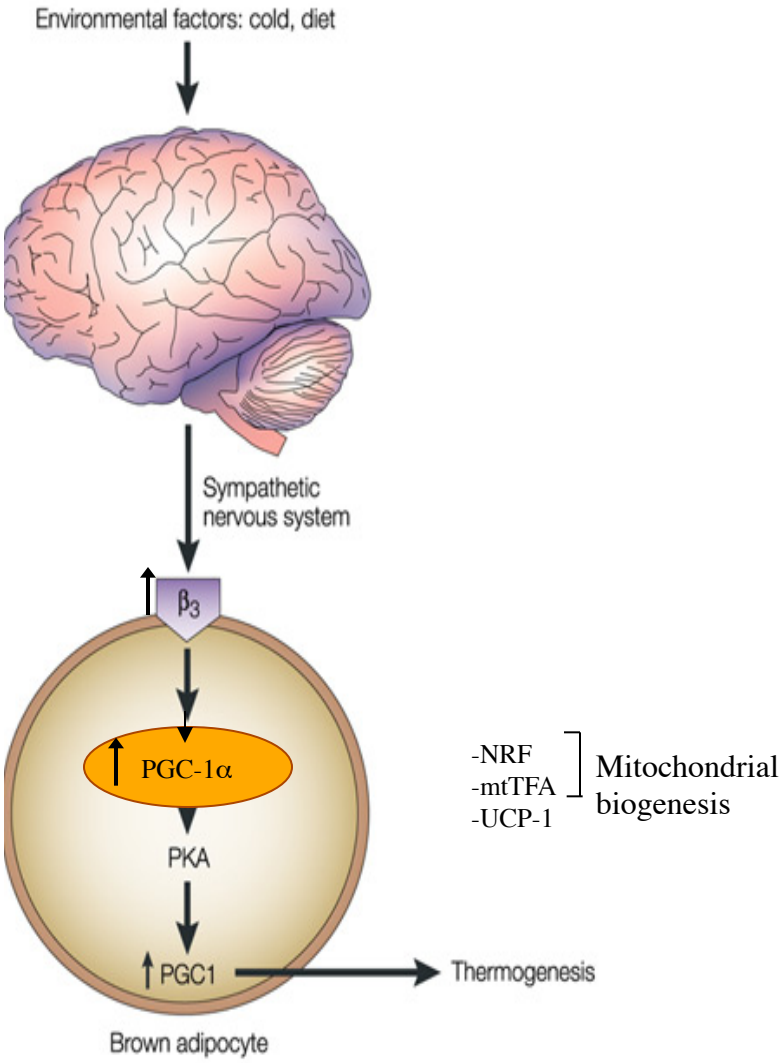
IRISIN : an exercise-induced myokine, stimulates conversion of white into brown adipocytes as well as increased mitochondrial biogenesis and energy expenditure

Obese subject
with very low BAT activity

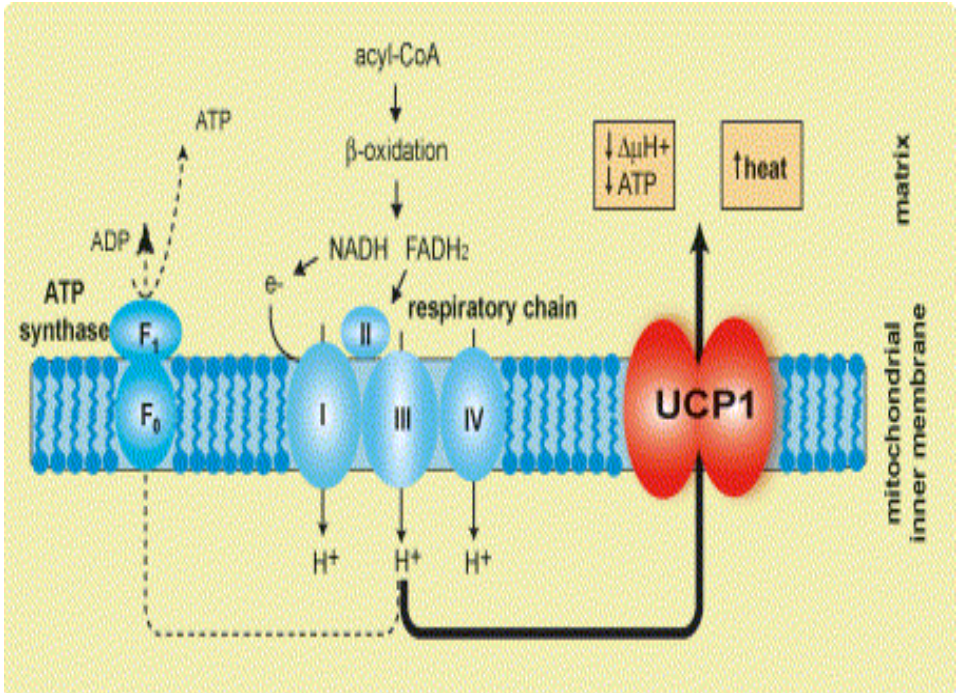


Van Marken Lichtenbelt et al, 2009 N.Engl. Med
Cypess et al, 2009 N.Engl. Med

Adaptative thermogenesis in brown adipocytes



Mitochondria inner Membrane



UCP1 is located in the mitochondrial inner membrane where it uncouples substrate oxidation from ATP synthesis, thereby dissipating energy as heat (adaptative thermogenesis)

Leptin and energy homeostasis

10 years : 10^6 kcalories

Leptin :

Link between food and physiology.

Hormone secreted by adipocytes and active in neurons and periphery

- **Controls food intake and body mass**

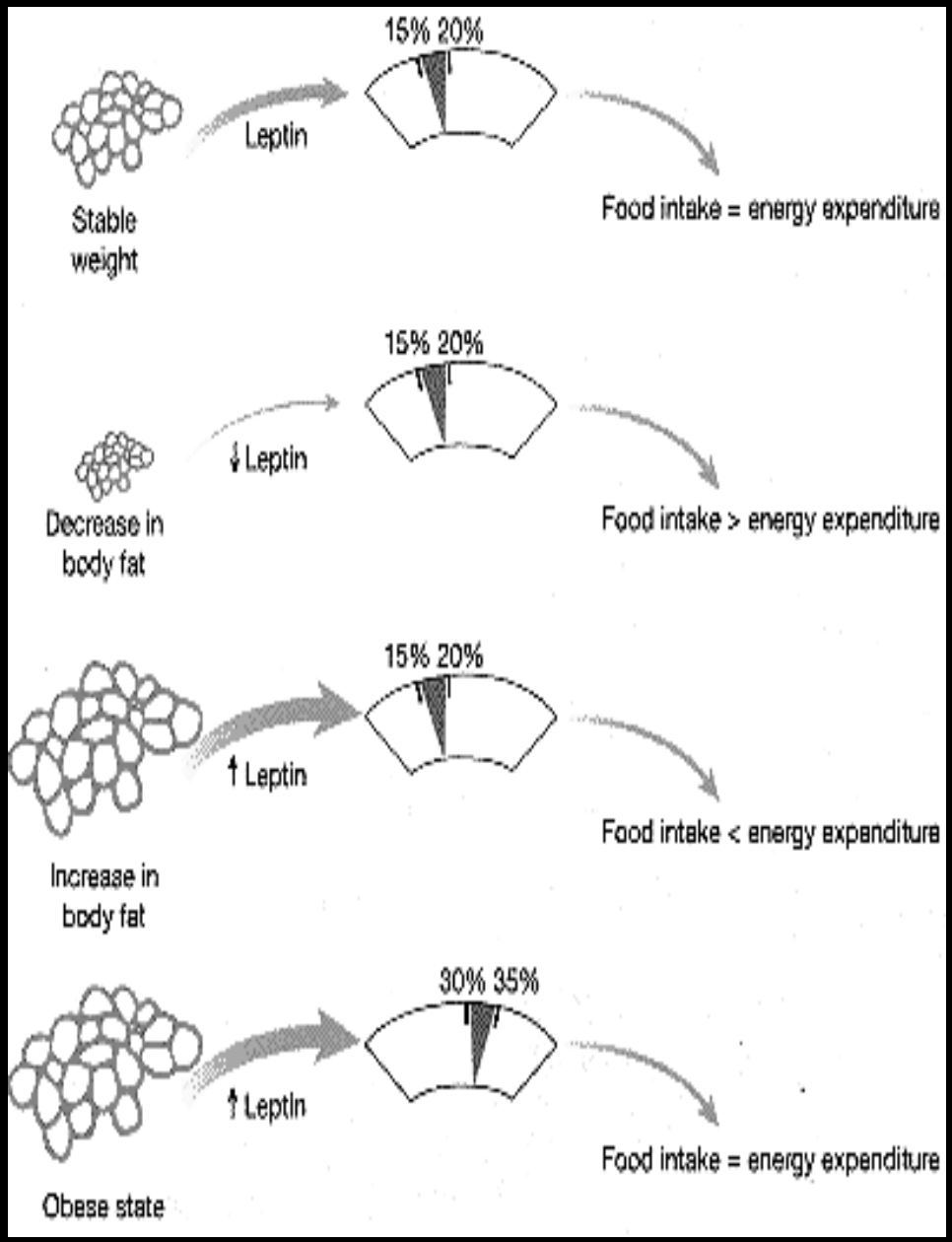
Obese individuals :

Decrease in the leptin sensitivity

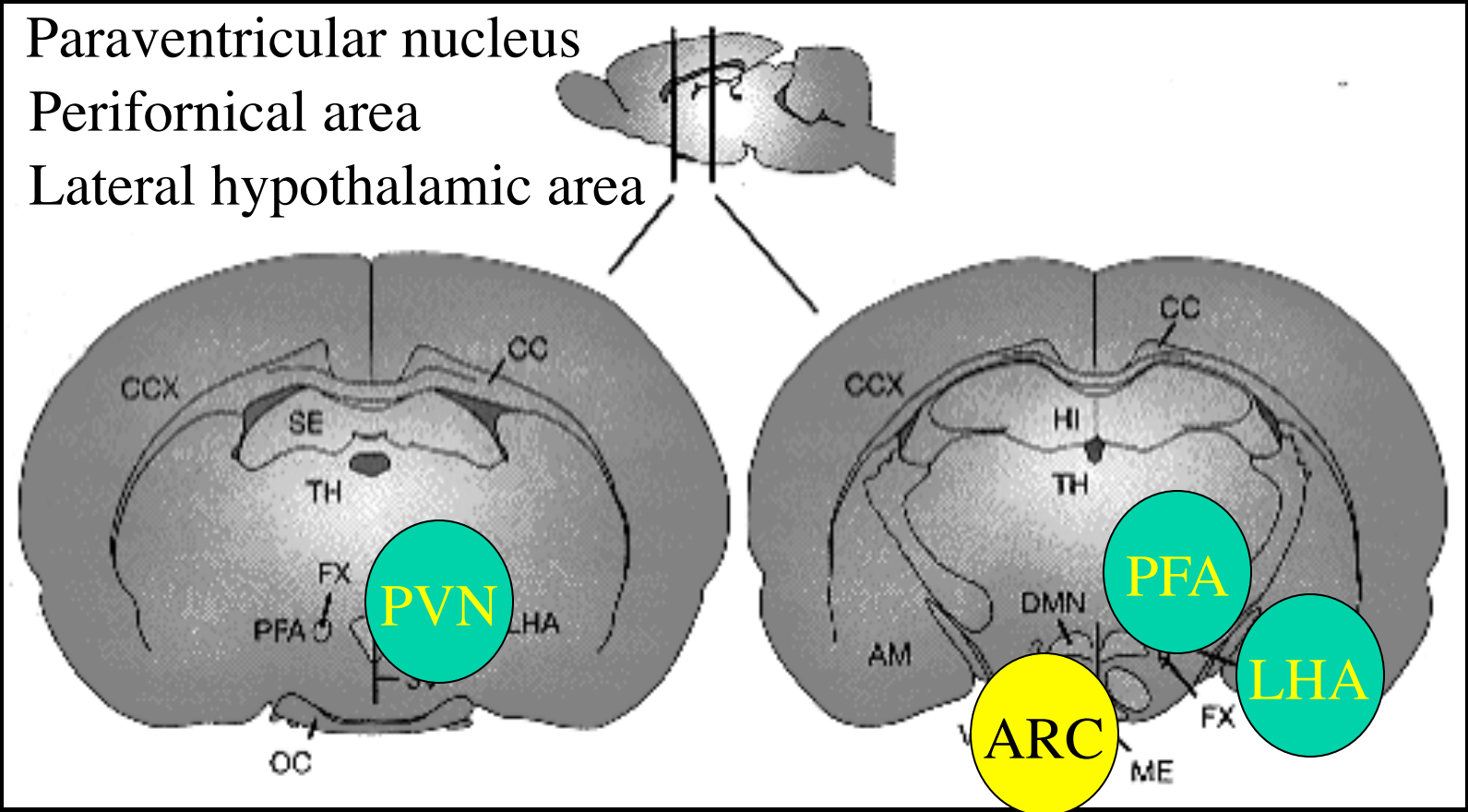
= resistance

- Reduction of passage through BBB (low in brain / plasma)

- SOCS-3

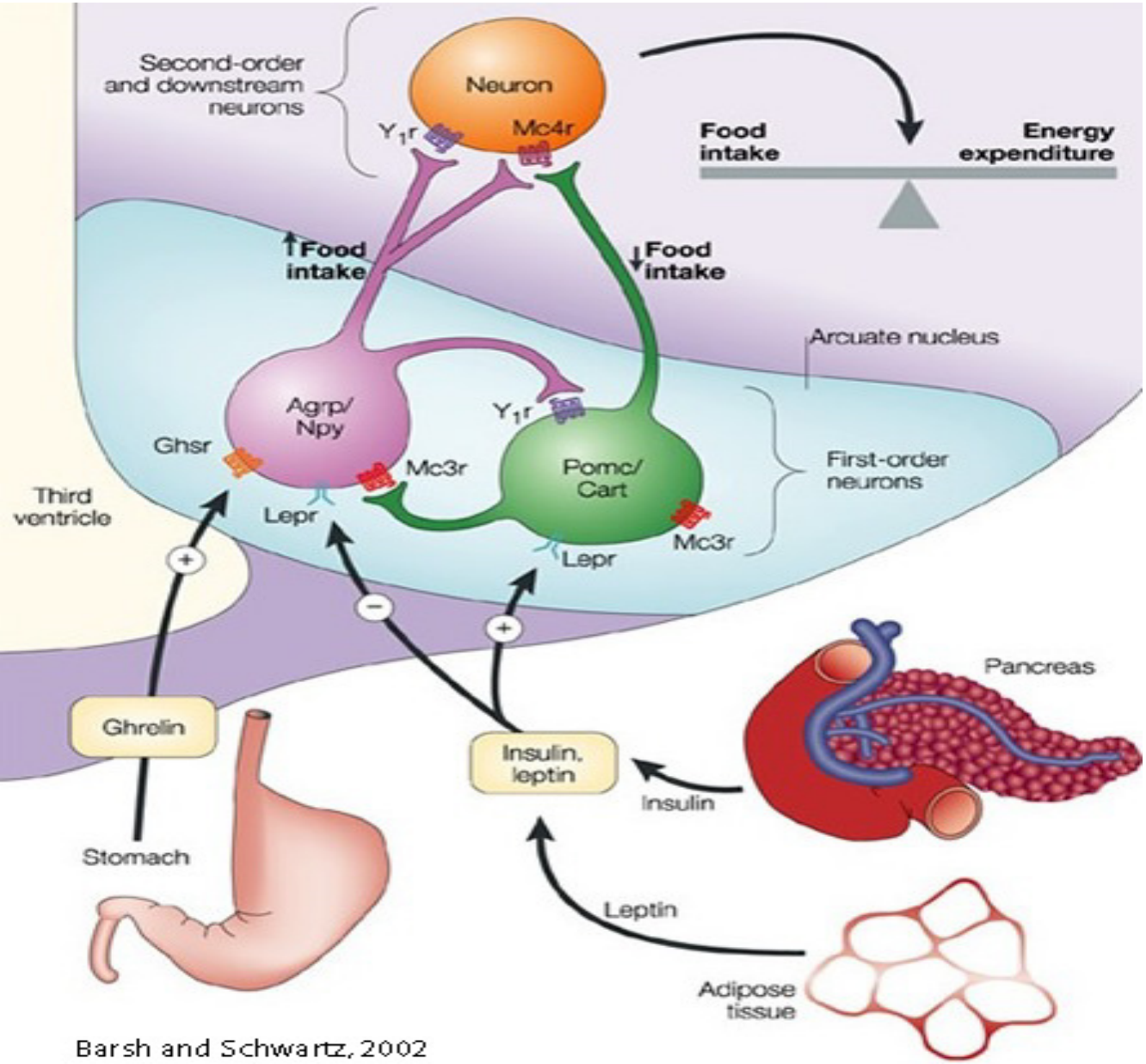


Major hypothalalmic regions implicated in adiposity signalling and food intake



The Arcuate (ARC) Nucleus acts as a sensory organ for peripheral signals of energy status.

Control of food intake and energy expenditure



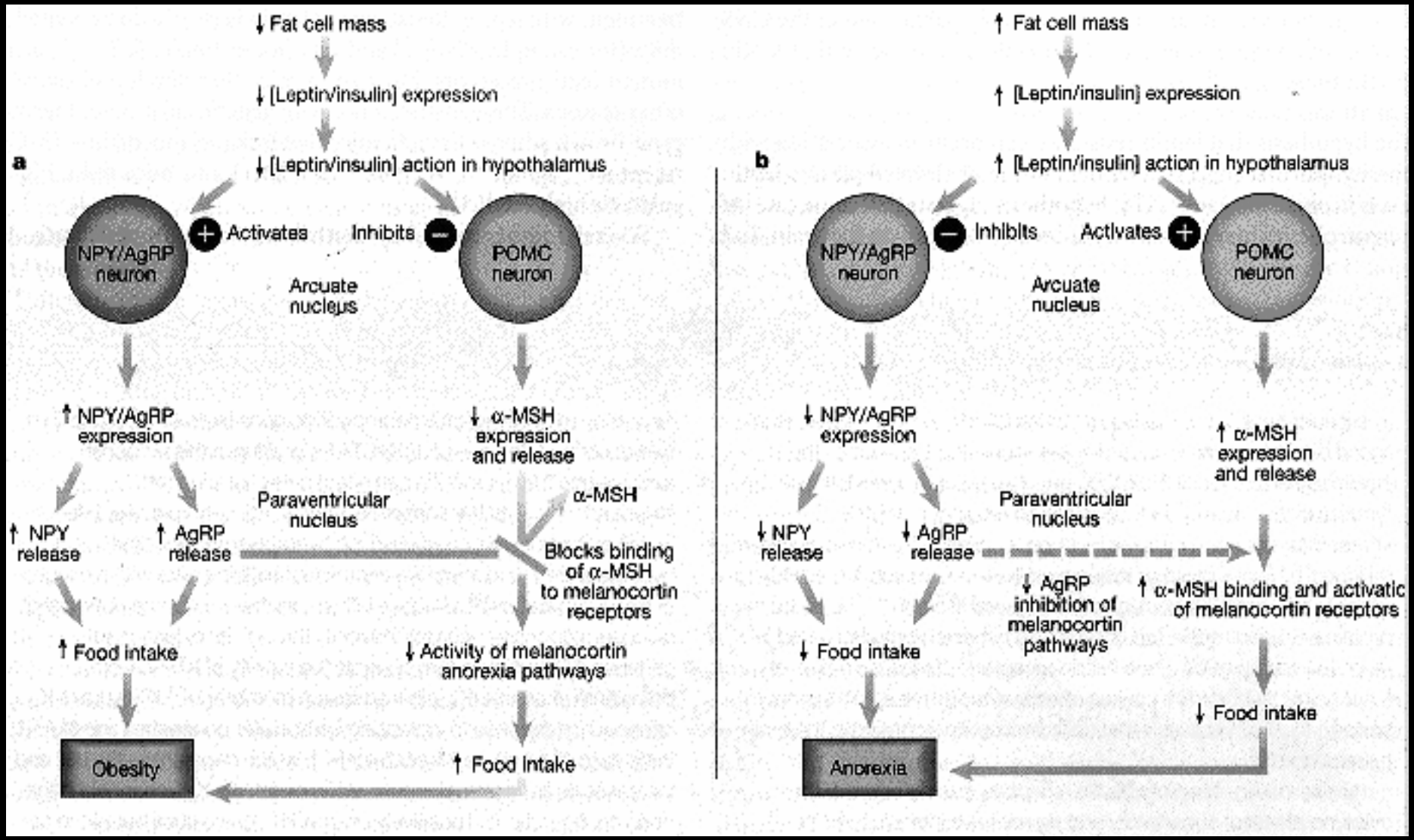
Hypothalamus : arcuate nucleus

Neuropeptides :

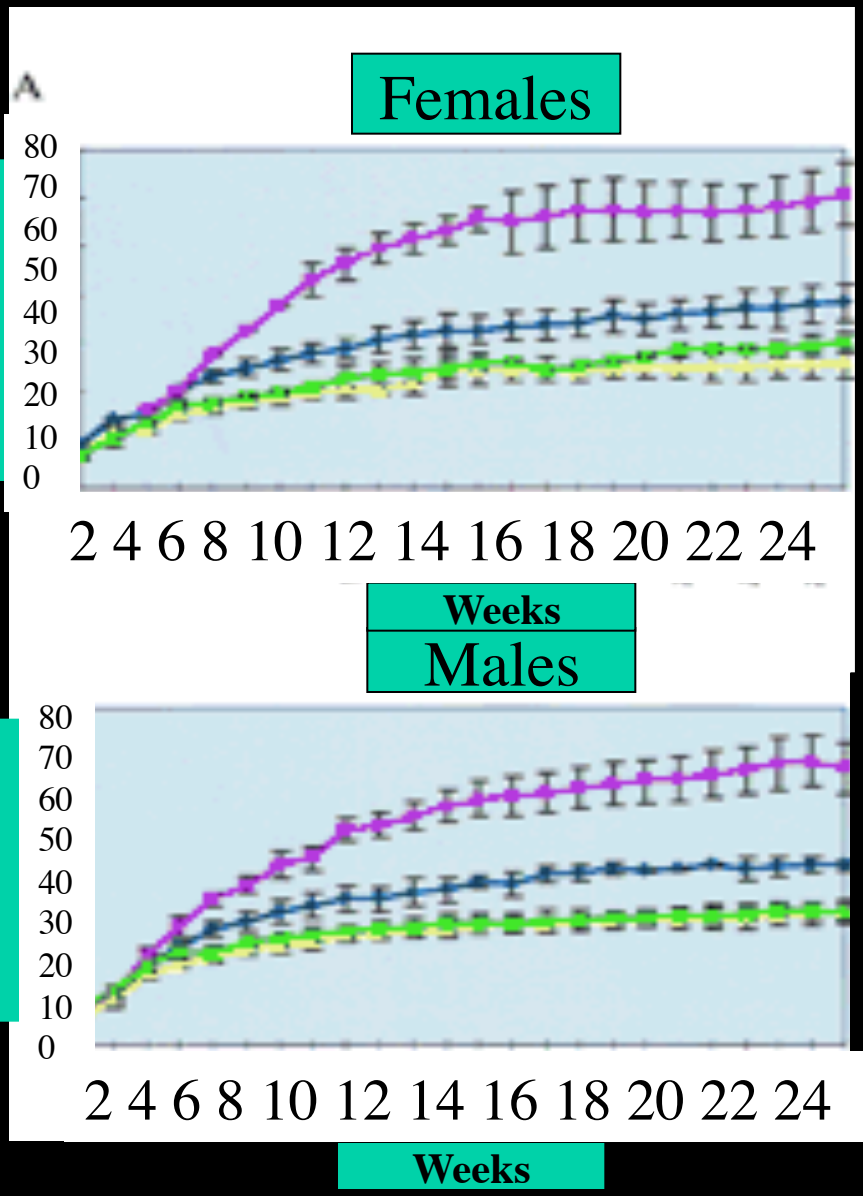
Agouti-related protein and neuropeptide Y (stimulates food intake and inhibit energy expenditure)

Propiomelanocortin/ cocaine and amphetamine-regulated transcript (inhibit food intake and stimulate energy expenditure)

Role of arcuate nucleus neurons in adiposity signaling



Phenotype of ob/ob TG mice



ob/ob (TG)

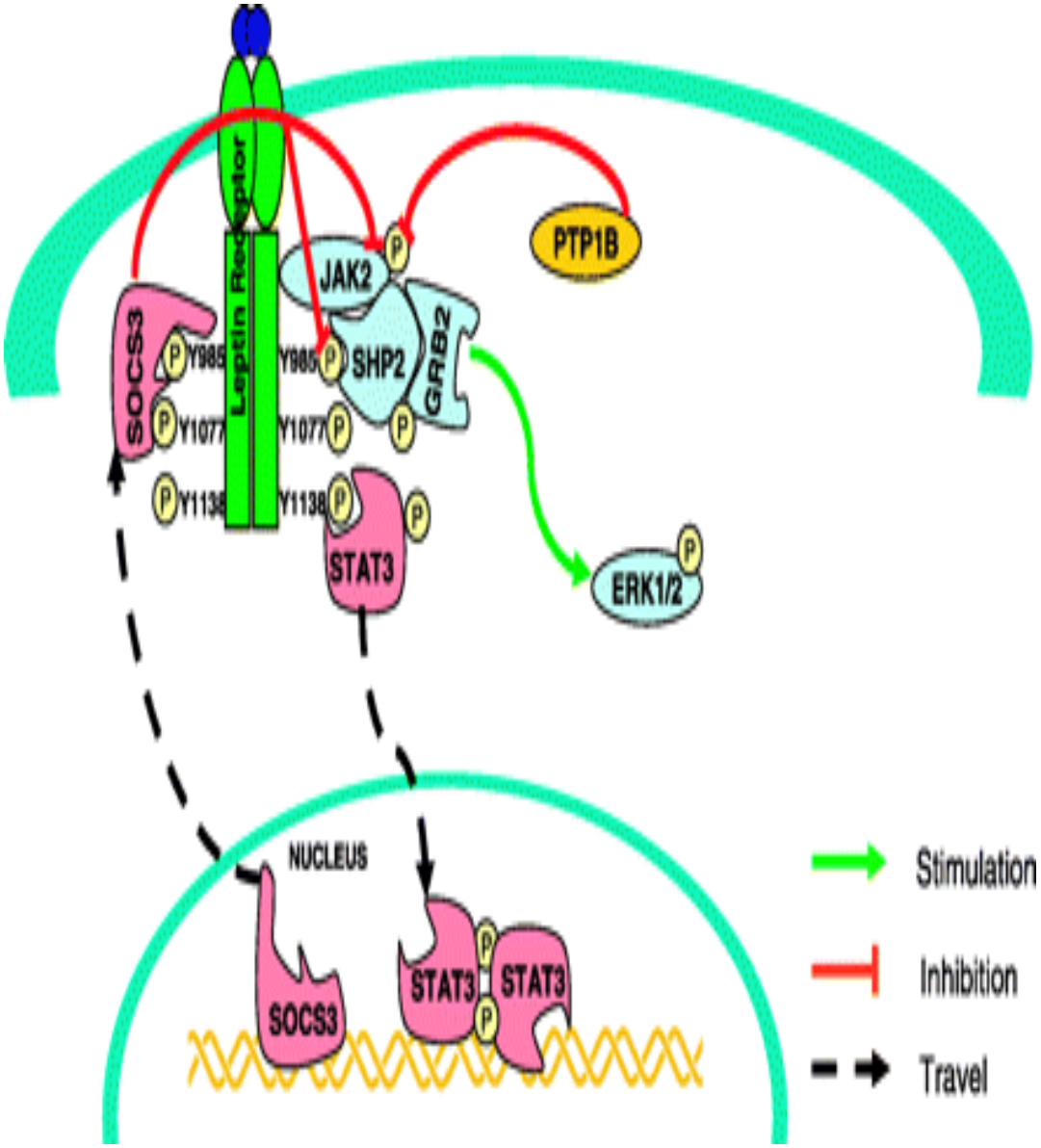
ob/ob (KO)

ob/+ (TG)

ob/+ (KO)

Leptin : the 16-kDa hormonal product of the obesity (*ob*) gene

Yang and Barouch, Circulation Research, 2007



The primary physiological role of leptin is to communicate to the central nervous system (CNS) the abundance of available energy stores and to restrain food intake and induce energy expenditure.

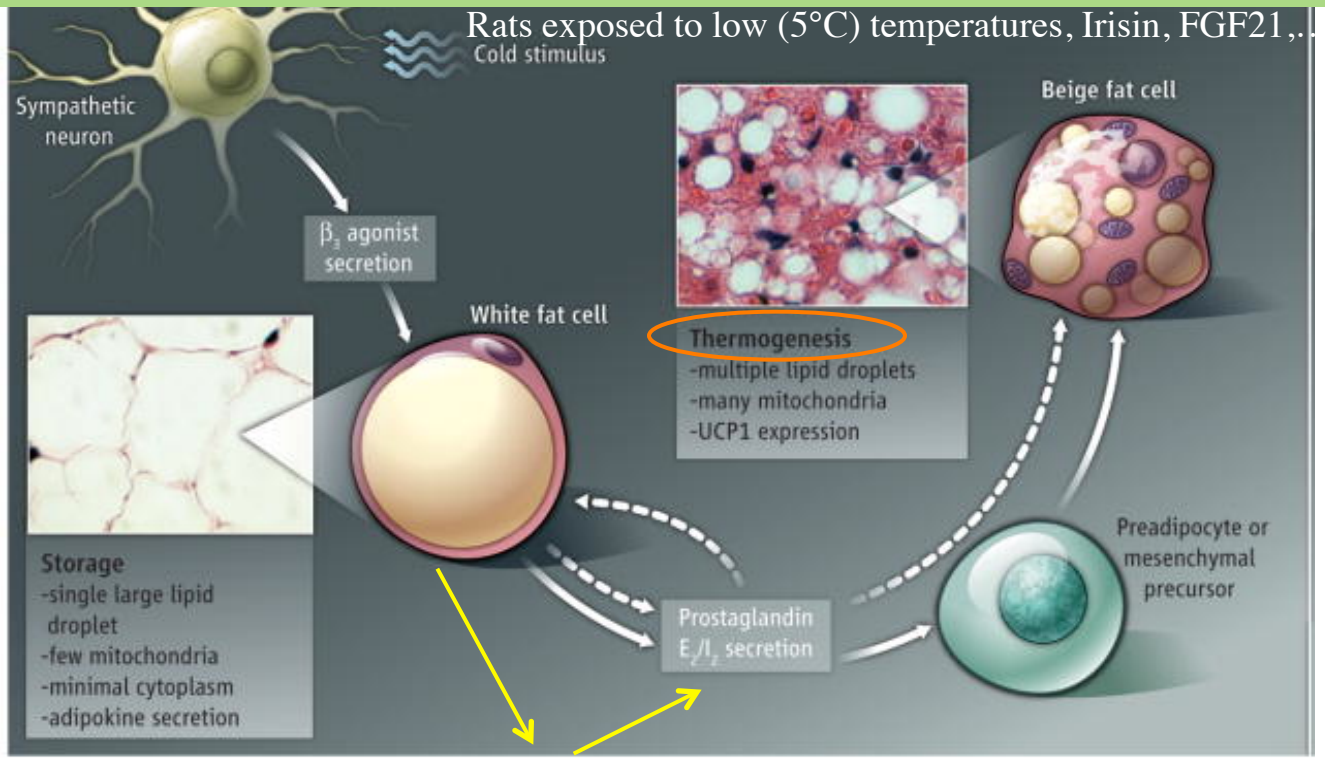
The absence of leptin therefore leads to increased appetite and food intake that result in morbid obesity.

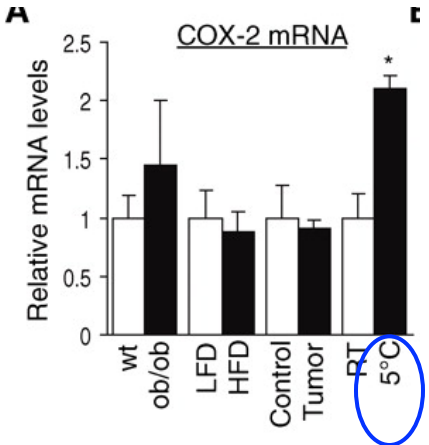
Notably, only rare cases of severe early childhood obesity have been associated with leptin deficiency.

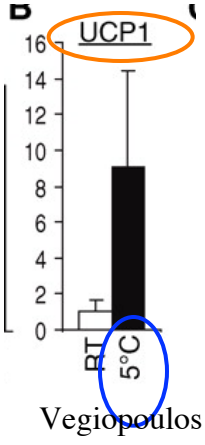
The remainder of the obese population typically have elevated leptin levels. The failure of leptin to induce weight loss in these cases is thought to be the result of leptin resistance (hyperleptinemia caused by deficit in the circulatory transport and/or in the signaling cascade).

SOCS3 : suppressor of cytokine signaling

Transdifferentiation from white fat cells to «beige» fat cells (brown-like adipocytes)







Vegiopoulos *et al*. Science 2010

Genetics and obesity

- **Polygenic trait : non mendelian quantitative phenotype**
- **Correlation factor BMI**

- **Twin pairs -**
- **Monozygotic twins : 0.74**
- **Dizygotic twins : 0.32**

- **Parental-**
- **Offspring : 0.19**
- **Adoptive : 0.06**

Obesity or diabetes occur as a result of genetic differences in alleles (QTL/G)

Speliote-E et al., Nature 2015, February 12; 518 (7538):197-206

ARTICLE + interactions with Diet, Exercise, Epigenetics

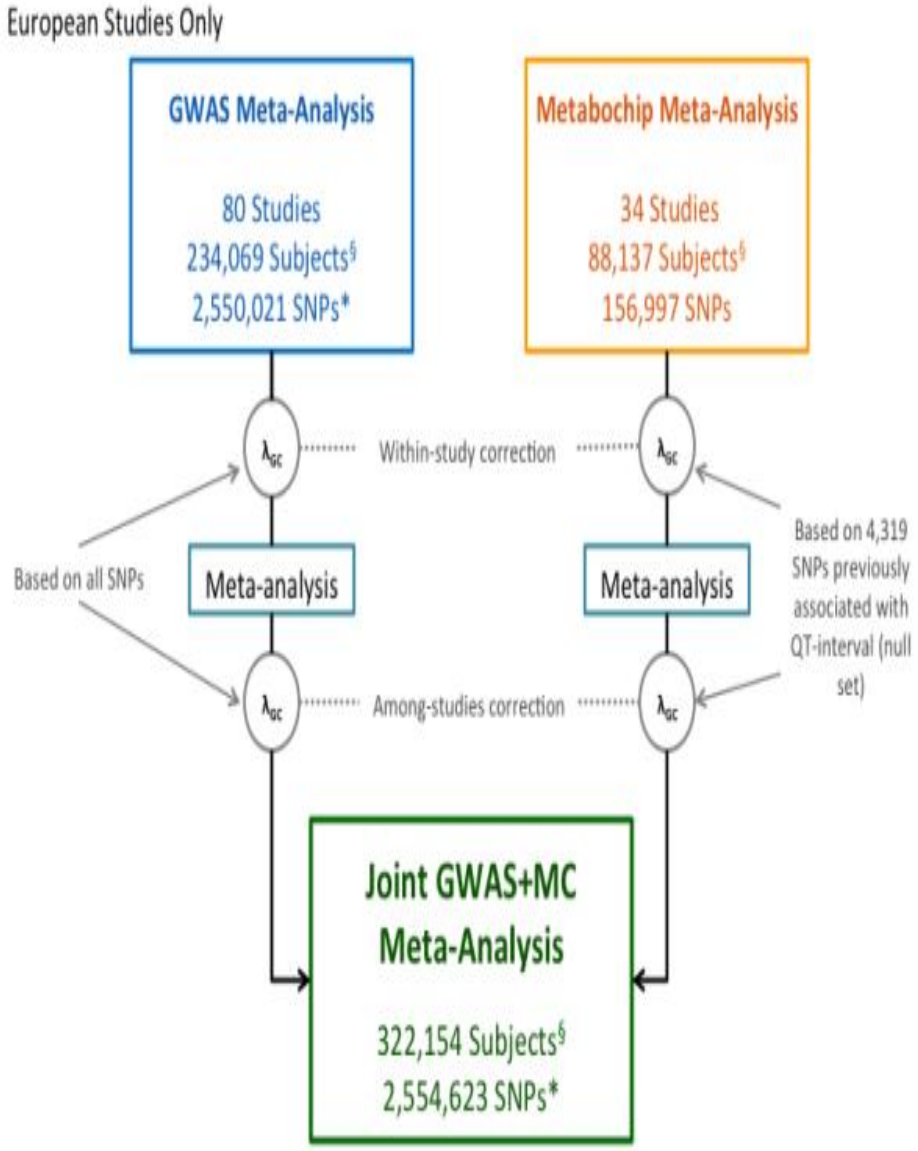
doi:10.1038/nature14132

New genetic loci link adipose and insulin biology to body fat distribution

A list of authors and their affiliations appears at the end of the paper

Body fat distribution is a heritable trait and a well-established predictor of adverse metabolic outcomes, independent of overall adiposity. To increase our understanding of the genetic basis of body fat distribution and its molecular links to cardiometabolic traits, here we conduct genome-wide association meta-analyses of traits related to waist and hip circumferences in up to 224,459 individuals. We identify 49 loci (33 new) associated with waist-to-hip ratio adjusted for body mass index (BMI), and an additional 19 loci newly associated with related waist and hip circumference measures ($P < 5 \times 10^{-8}$). In total, 20 of the 49 waist-to-hip ratio adjusted for BMI loci show significant sexual dimorphism, 19 of which display a stronger effect in women. The identified loci were enriched for genes expressed in adipose tissue and for putative regulatory elements in adipocytes. Pathway analyses implicated adipogenesis, angiogenesis, transcriptional regulation and insulin resistance as processes affecting fat distribution, providing insight into potential pathophysiological mechanisms.

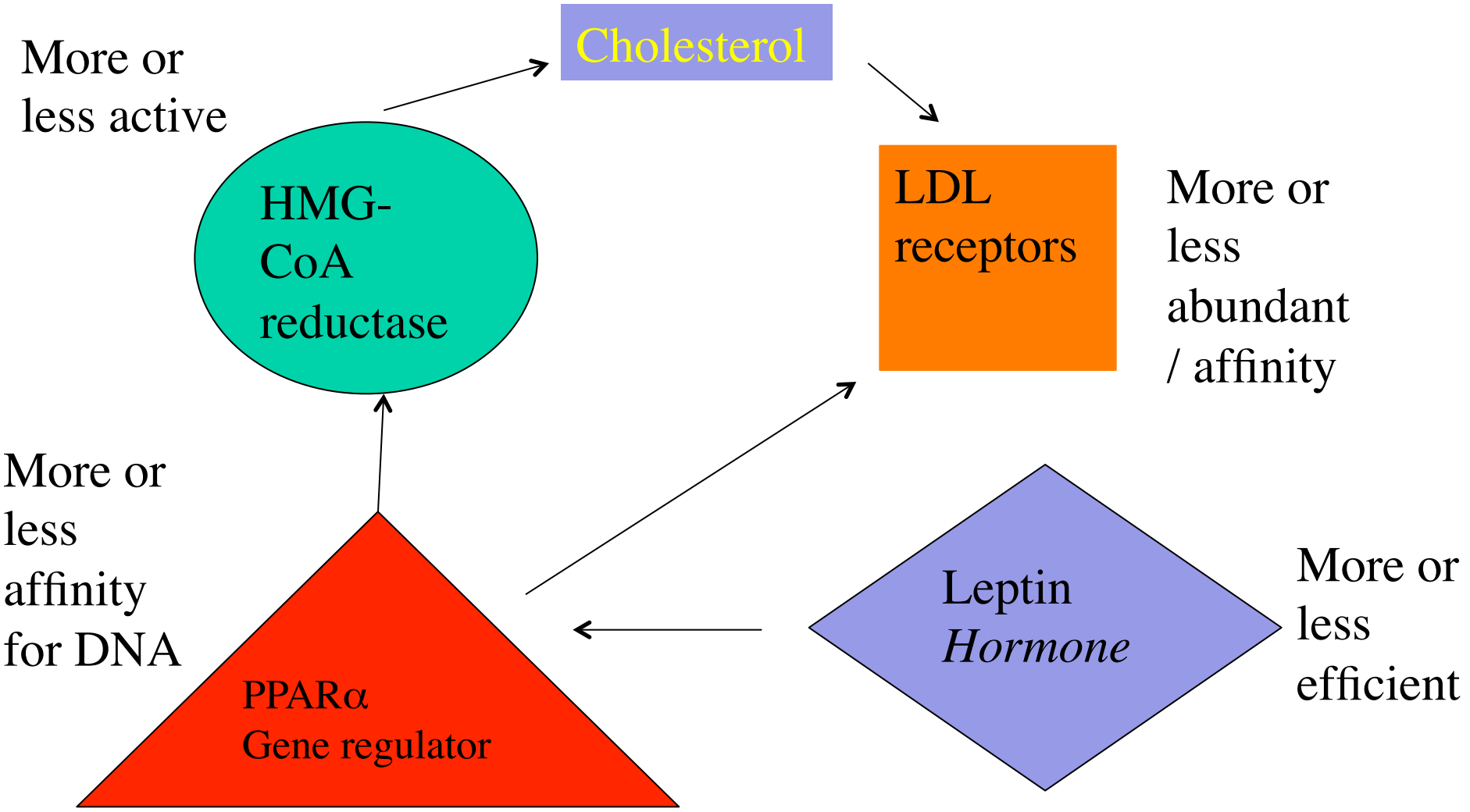
Major Conclusions



- The study, involving more than 300,000 people, highlights 97 gene variants : 53 new genes affecting body mass.
- Many in the appetite control / basal metabolism
- Some people are addicted to food and find hard to suppress their appetite.
- The analysis reinforces the idea that weight is influenced by a very large number of genes each making a small contribution.
- Even the 97 genes variants shown to have the most powerful effect together only explain about 3% of the variation in BMI across the population.
- New development for therapies
- Evolution– the so-called “thrifty gene” hypothesis: less energy for physical and mental exertion, storing energy in fat reserves would help during times of scarcity.
- On the planet for the past five million years, but only had great food supplied for the past 100 years.
- We are not genetically ideally adapted to our environment today.

Complex trait : cholesterolemia
Variants with (partial) gain or loss of functions

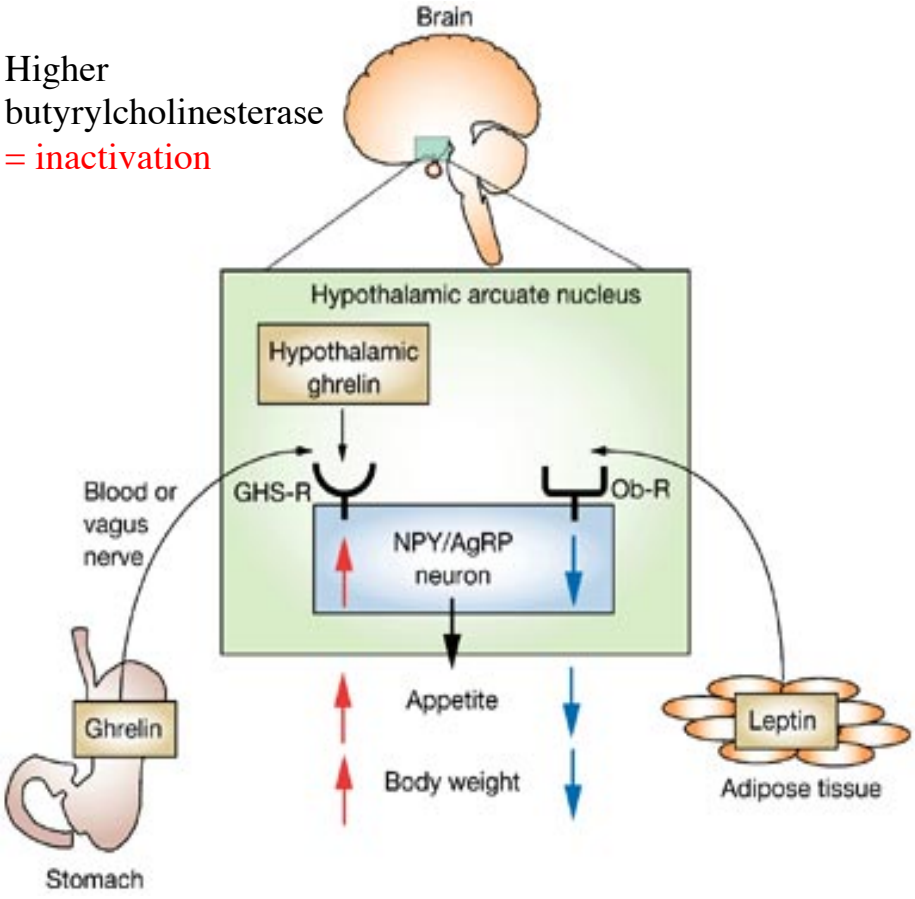
Combination of subtle gene changes add up to produce a disease trait
Gene interactions : favorable, defavorable or neutral



Examples of loci associated with obesity

1) Point mutation in *GHRL* gene (Leu72Met)

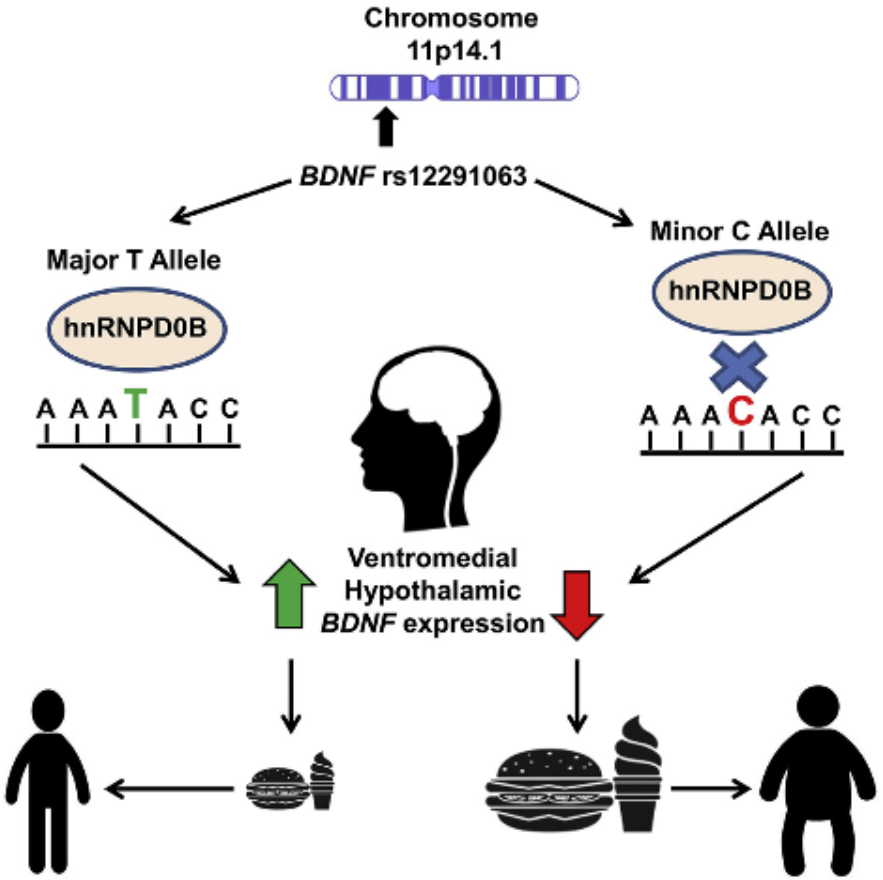
Higher butyrylcholinesterase = inactivation



Ukkola et al., 2011, BCEM

2) SNP in *BDNF* gene

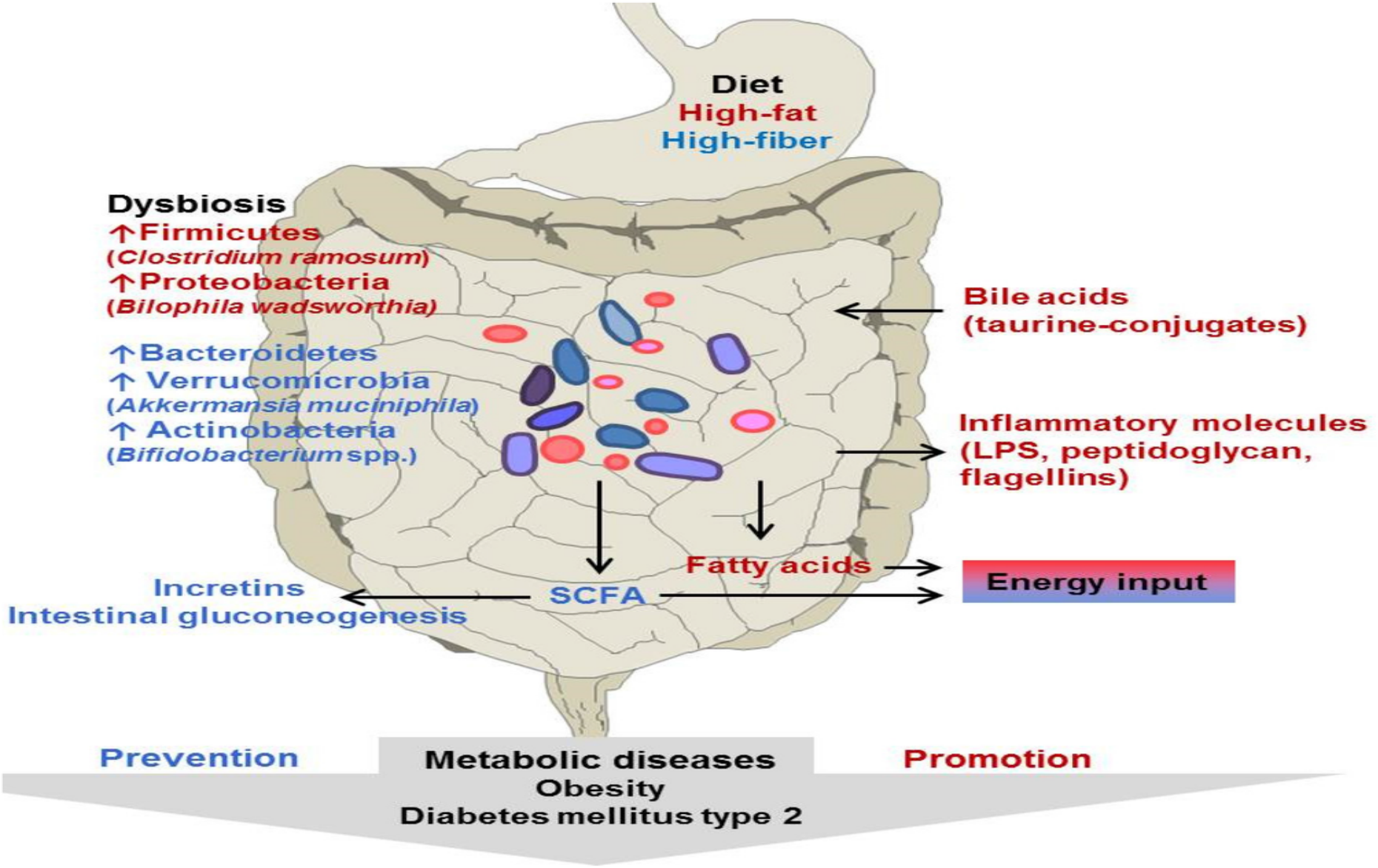
Brain-derived neurotrophic factor



Mou et al., 2015, Cell Reports

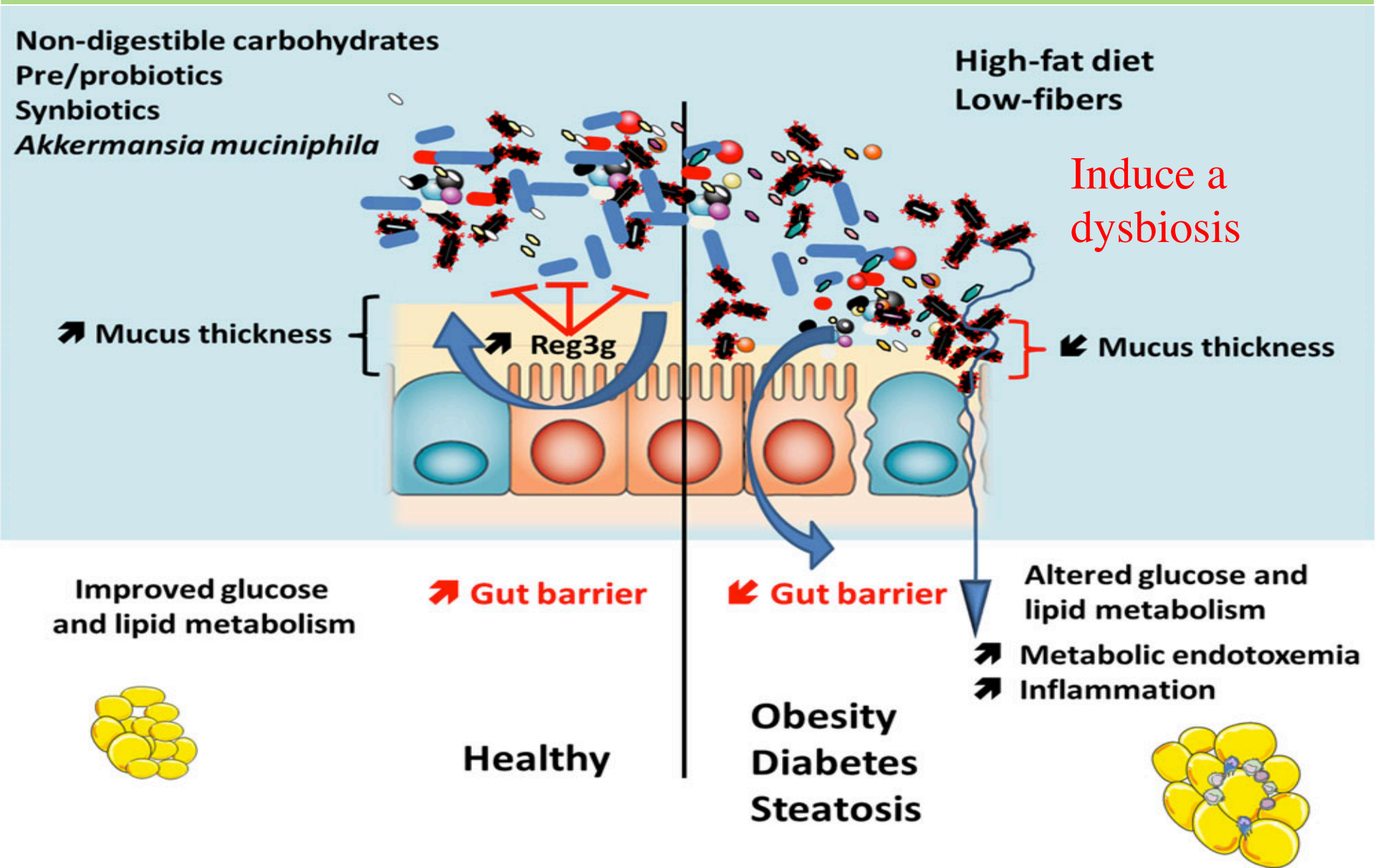
Hypothetical interplay between diet, gut microbiota and host in prevention and promotion of metabolic diseases

(Woting and Blaut, Nutrients, 2016, 8(4), 202)



Crosstalks between host and microbes: impact on metabolism

P. Cani and A. Everard, *Mol. Nutr. Food Res.* 2016, *60*, 58–66



Food

Non-digestible nutrients

ITF – GOS – AX – XOS | Chitin-glucan | Phenolic compounds

Inulin-type fructans, galactooligosaccharides,arabinoxylan, arabinoxylan oligo

Changes in gut microbiota

↑ *Bifidobacterium* spp. ↑ *Lactobacillus* spp. ↑ *Collinsenlla* spp. ↑ *Roseburia* spp.
↑ *Akkermansia muciniphila* ↑ *Faecalibacterium prausnitzii* ↑ *Bacteroides-Prevotella* spp.

Targeted organs

↑ L cells
↑ Tight junctions (barrier)
↑ GLP-1, GLP-2, PYY
Regulation of eCB system tone

↓ Lipogenesis
↓ Inflammatory markers

↓ PPARg/GPR43
↓ Inflammatory markers
Regulate eCB system tone
Change apelinergic system tone

↑ Insulin sensitivity
↓ Inflammatory markers

Molecular targets

Metabolic consequences related to obesity

↓ Glycemia ↓ Fat mass ↓ Steatosis ↓ Appetite ↓ Lipemia
↓ Insulin resistance ↑ Glucose tolerance ↓ Inflammation ↓ Metabolic endotoxemia
Modulation of the endocannabinoid and the apelinergic system tone

Geurts et al., *Beneficial Microbes, March 2014; 5(1): 3-17*

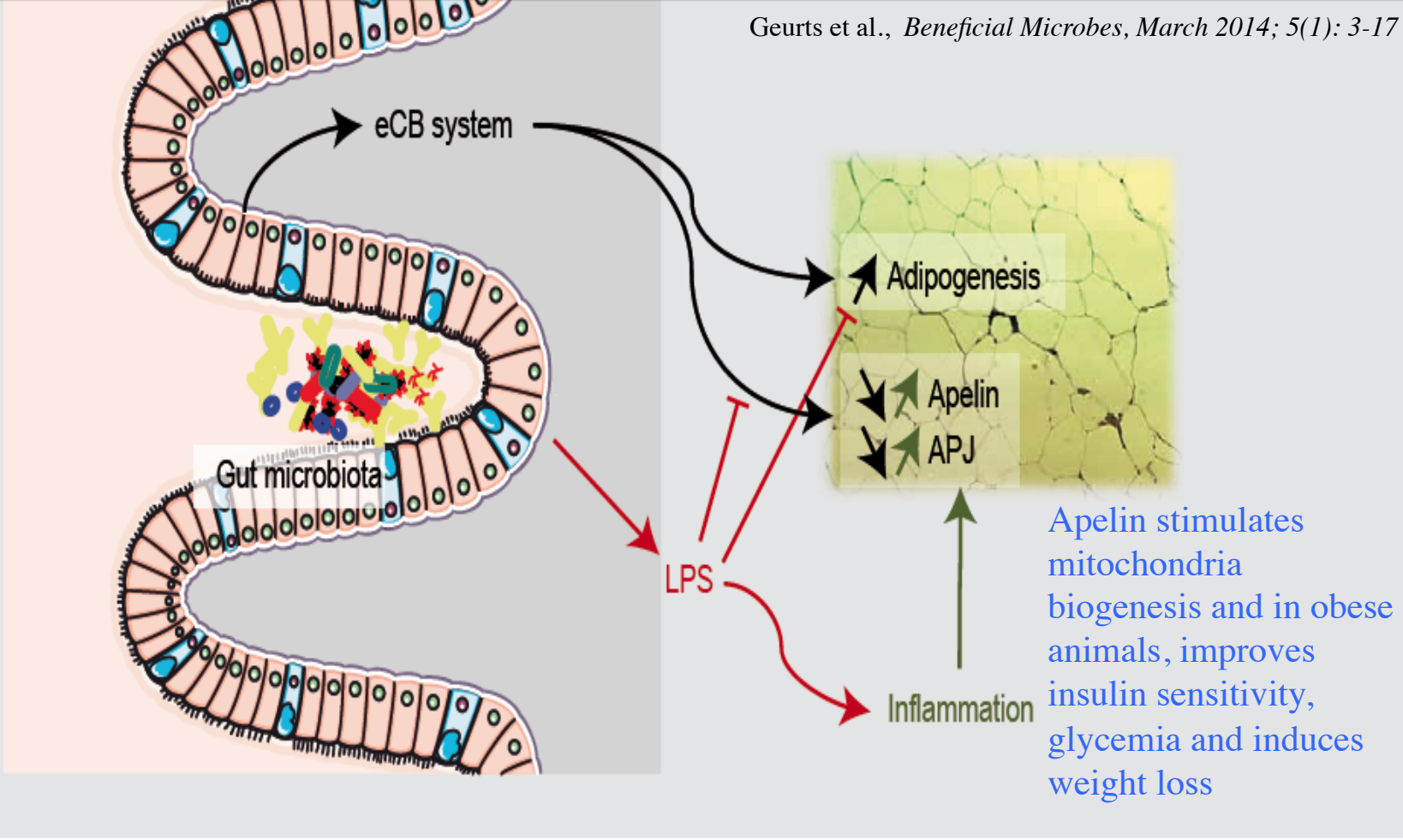


Figure 2. Crosstalk between the gut microbiota, the endocannabinoid system, the apelinergic system and impacts of metabolic endotoxaemia on adipose tissue development. In physiological situations, the endocannabinoid (eCB) system tone reduces the levels of apelin and apelin receptor (APJ) mRNA in adipose tissues, whereas the inflammatory tone increases these markers. Endocannabinoids increase the adipogenesis processes. In obesity, both the eCB system and the inflammatory tone are increased and associated with metabolic endotoxaemia (i.e. circulating lipopolysaccharide (LPS)). In this pathological condition, LPS completely abolished the effects of endocannabinoids on adipogenesis and the apelinergic system, suggesting that both eCBs and LPS are implicated in adipose tissue metabolism.

Obesity Management (3 or 6 months)

Treatment of obesity starts with comprehensive lifestyle management (diet, physical activity, behavior modification)

Reduction of caloric intake and **physical activity**
Reduction of 500-1000 kcal/day + 150 min of moderate activity and 75 min of intense activity/week

Effective management of obesity must be based on a partnership between a highly motivated patient and a committed team of health professionals.

* physician, a psychologist or psychiatrist, physical and exercise therapists, dietitians,

Gain : modest weight loss between 5% and 10% for the long-term- good for co-morbidities improvement.

Diet, exercise, and behavioral modification : should be included in all obesity management approaches for body mass index (BMI) of 25 kg/m ^{2} or higher.
Pharmacotherapy (GLP-1 analogs, TZD : glitazones, metformin, ACE inhibitor,…) : for BMI of 27 kg/m^2 or higher with comorbidity or BMI over 30 kg/m^2
Bariatric surgery : for BMI of 35 kg/m^2 with comorbidity or BMI over 40 kg/m^2 : reduction of BM by 20-30 %-sustained.

Stuart's Behavioral Approach : ABC Model

A ----------> B ----------> C

Antecedent Behavior Consequence

Conventional Food

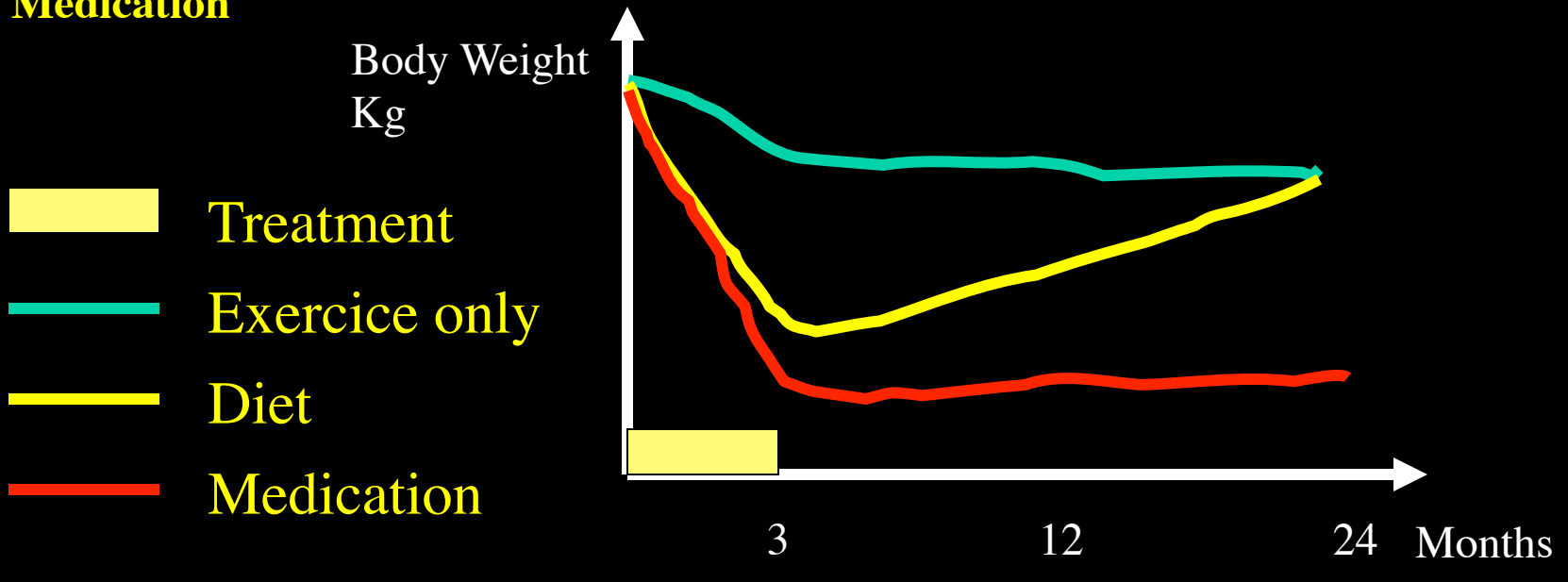
↓

Decrease Intake
Increase Energy Expenditure / Behavior
Medication

Very Low Calorie Diet

↓

Not Effective / Long Term



Treatments of overweight and obesity in adults

overweight | obese

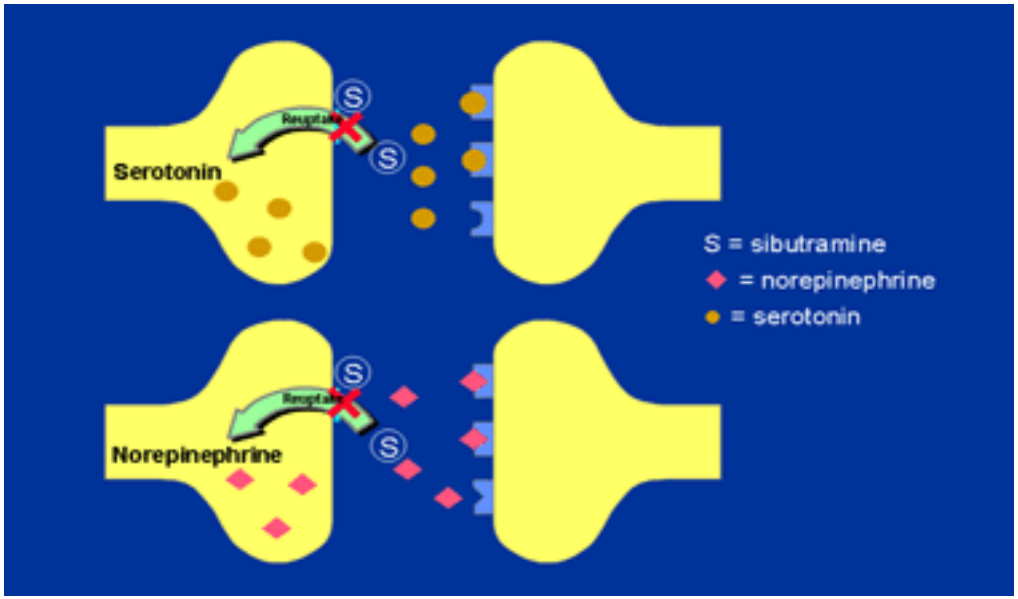
	BMI category				
Treatment	**25–26.9**	**27–29.9**	**30-34.9**	**35–39.9**	**≥ 40**
Lifestyle therapy: Diet, physical activity, and behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				With comorbidities	

- Prevention of weight gain with lifestyle therapy is indicated in any patient with a BMI ≥ 25 kg/m², even without comorbidities, while weight loss is not necessarily recommended for those with a BMI of 25–29.9 kg/m² or a high waist circumference, unless they have two or more comorbidities.
- Combined therapy with a low-calorie diet (LCD), increased physical activity, and behavior therapy provide the most successful intervention for weight loss and weight maintenance.
- Consider pharmacotherapy only if a patient has not lost 1 pound per week after 6 months of combined lifestyle therapy.

The + represents the use of indicated treatment regardless of comorbidities.

Sibutramin: mechanism of action

Serotonin and norepinephrine re-uptake inhibitor (SNRI) in the CNS increasing the sensation of satiety



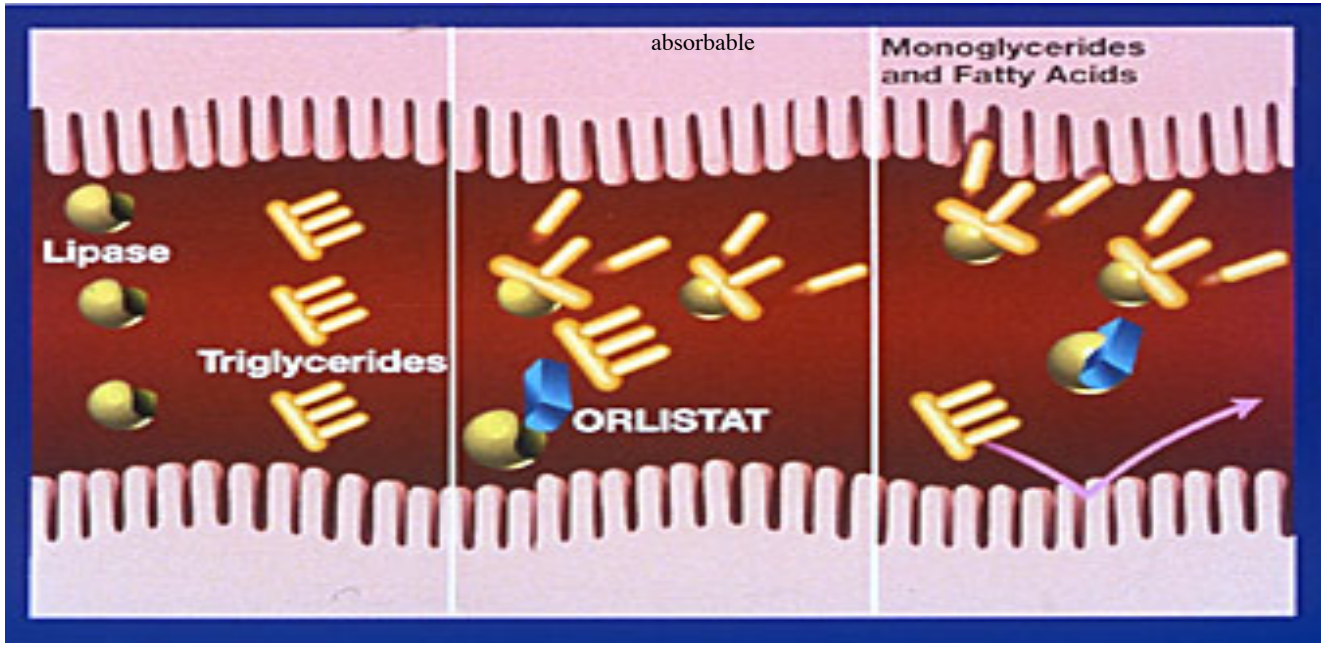
Adapted from Ryan DH, et al. Obes Res. 1995 (suppl.4): 553S-559S

Average weight loss: 5-10 % of the starting body weight after one year of treatment.

Adverse Effects: Increase in heart rate and blood pressure, headache, dry month, constipation and insomnia.

Orlistat: mechanism of action

Decreases fat absorption, inhibits pancreatic lipase



Orlistat:

- with prescription (120 mg)
- without prescription (60 mg) + lifestyle therapy

Average weight loss: 5-10 % of the starting bodyweight after one year of treatment.

Adverse Effects: Decrease in absorption of fat-soluble vitamins, soft stools and bowel urgency and flatulence.

Risk of hepatic lesions and renal failure

L’alimentation bio réduit le risque de surpoids et d’obésité

Rédaction en ligne
Mis en ligne mardi 26 avril 2016, 23h57

Lire aussi : L’alimentation bio réduit le risque de surpoids et d’obésité

La méditation réduit le risque d'obésité

Le 04 décembre 2015 à 11h07 - Mis à jour le 04 décembre 2015 à 13h00 - par Agathe Mayer

Les techniques de relaxation permettent de réduire le stress, et diminuer les risques de surpoids ou d'obésité par deux. Elles doivent être pratiquées régulièrement pour être efficaces.

»Dernières actu

Les Américains maigrissent très vite, mais c'est une Française qui a battu le record !

Mercredi, 27 Avril, 2016

Les journaux de l'autre côté de l'Atlantique décrivent les histoires de personnes obèses, qui ont perdu beaucoup de poids grâce à une méthode élaborée par des diététiciens du Minnessota. Même les femmes et les hommes les plus résistants aux régimes et aux exercices, en appliquant leur méthode, perdent de 10 à 14 kilos en un mois.

Cependant, jusqu'à présent le meilleur résultat revient à une française. Marie, 28 ans, n'a laissé aucune chance aux Américains - elle à perdu **24kg en moins de deux mois** , sans faire de régime ni d'exercices ! Malgré une perte de poids si drastique, elle reste en bonne santé, elle maintient un poids stable depuis 5 mois et elle est plus heureuse que jamais.

http://actualitesendirect.com/33/sante/jai-senti-que-la-graisse-sevapore-de-mon-

Weight-loss-associated morbidity

Although obesity in itself is associated with increased morbidity and mortality, massive, poorly monitored weight loss and/or weight cycling can have equally dire consequences.

Among the important potential complications to watch out for in the setting of weight loss are the following:

Cardiac arrhythmias

Electrolyte derangements : Hypokalemia (low potassium < 3.5 mEq/L)

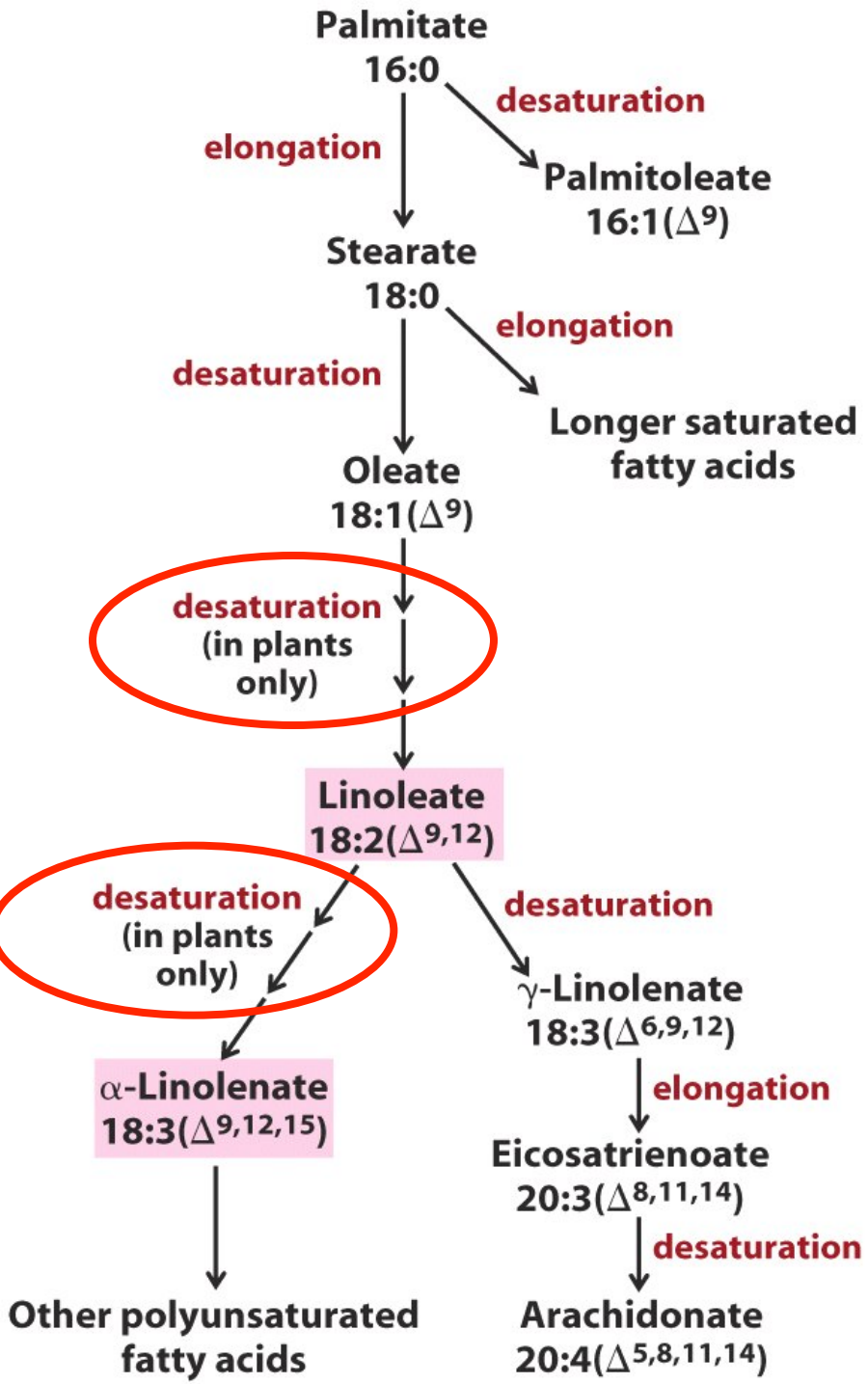
Hyperuricemia

Psychological sequelae : Including depression and the development of eating disorders (particularly binge-eating disorders)

Cholelithiasis : Gallstones are concretions that form in the biliary tract, usually in the gallbladder

Thank you for your attention…

Time for questions…



In summary: elongation/ saturation from palmitate

Elongation : saturated FA of longer chain by further addition of acetyl groups (FA elongation systems present in the smooth ER and mitochondria)

Palmitoyl-CoA ---> Stearoyl-CoA

Different enzymes (than in synthesis) and CoA rather than ACP but reactions are similar to the reactions involved in palmitate synthesis :

** donation of 2 C from malonyl-CoA followed by a reduction, a dehydratation, and a reduction to the saturated 18-C product*

Amino Acids

- Bacteria can synthesize all 20
- Mammals require some in diet

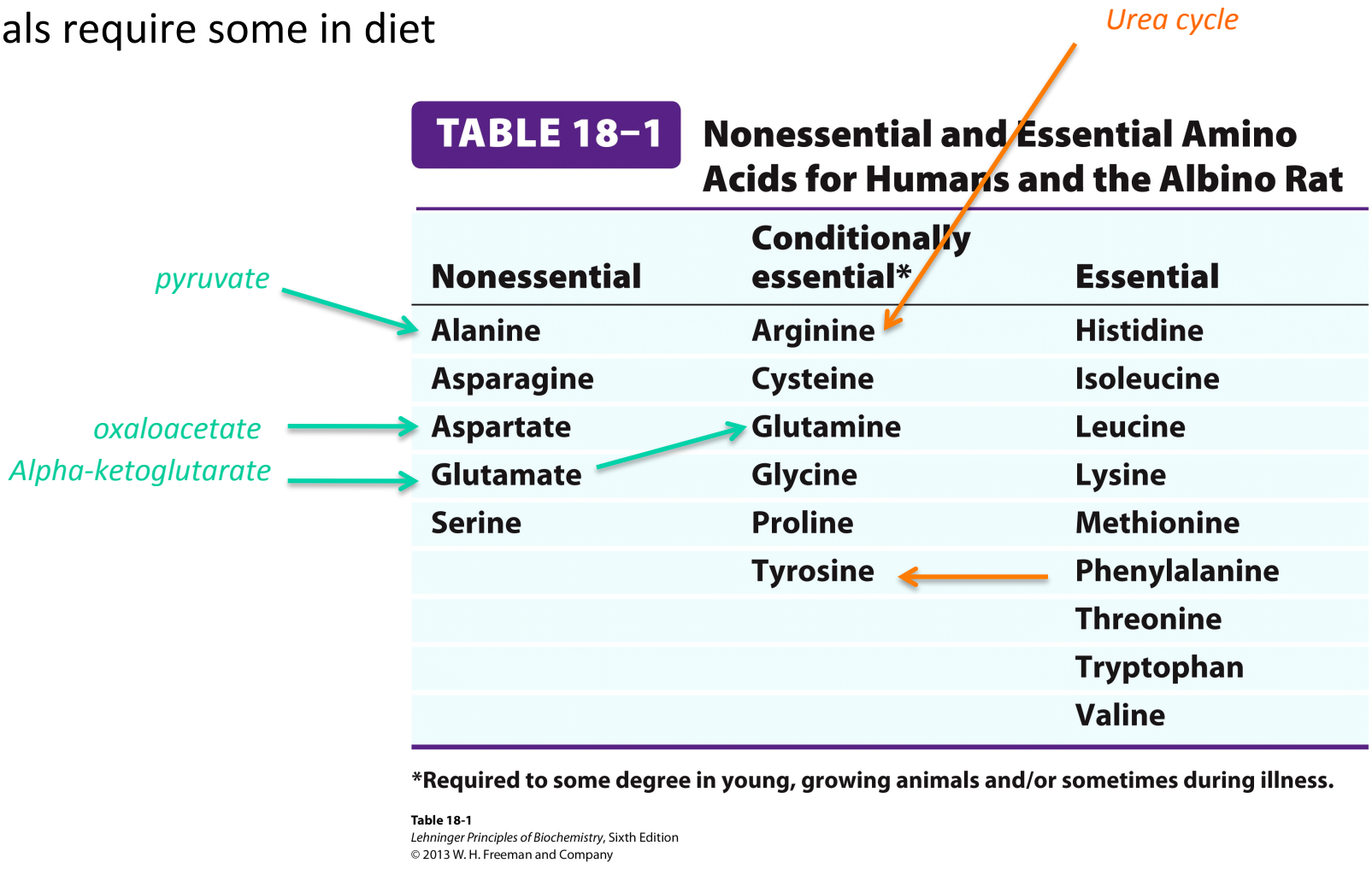


TABLE 18–1 Nonessential and Essential Amino Acids for Humans and the Albino Rat

Nonessential	Conditionally essential*	Essential
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

*Required to some degree in young, growing animals and/or sometimes during illness.

Table 18-1
Lehninger Principles of Biochemistry, Sixth Edition

Summary of Amino Acid Catabolism

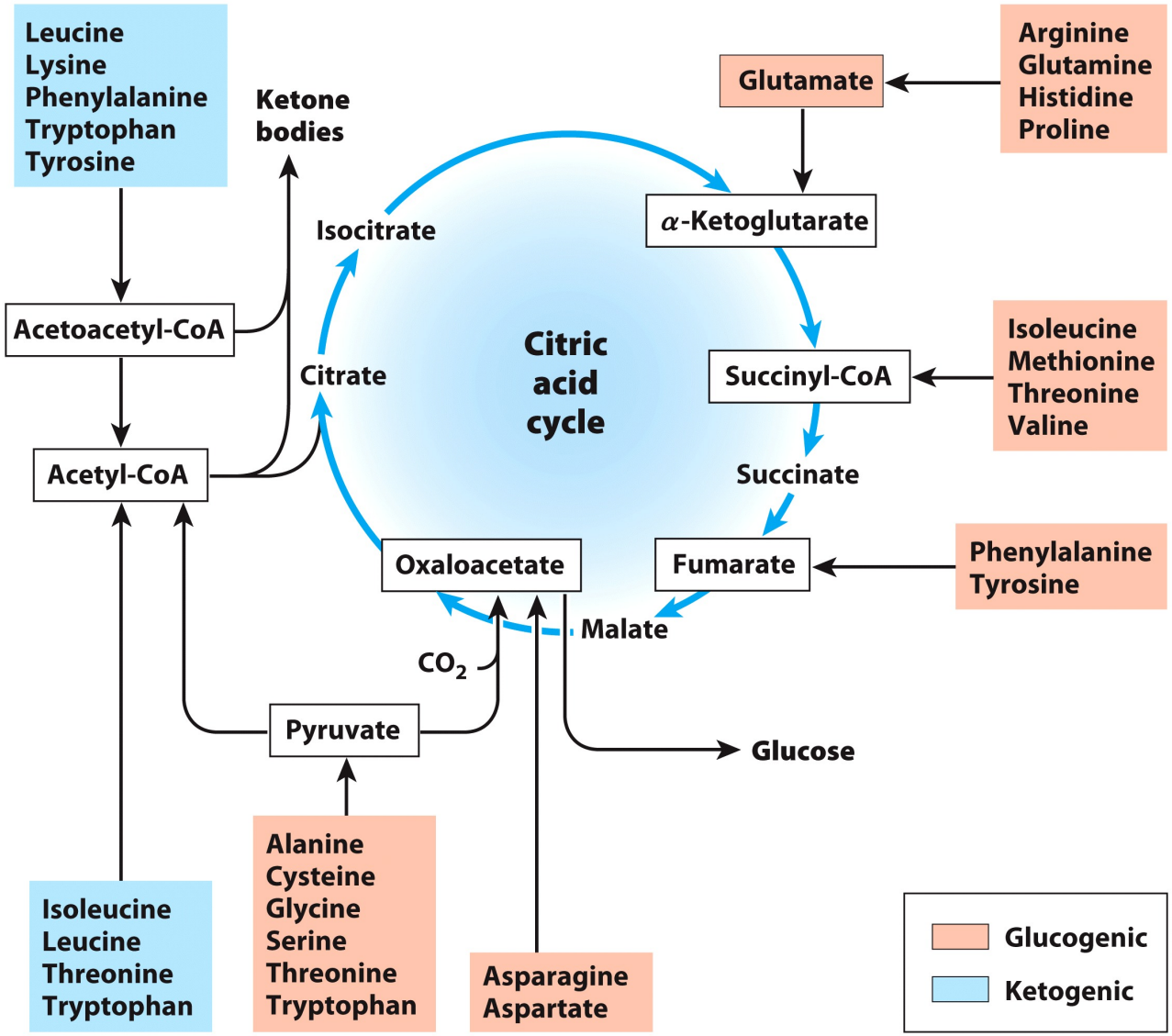


Figure 18-15
Lehninger Principles of Biochemistry, Sixth Edition

FIGURE 18–15 Summary of amino acid catabolism.
Amino acids are grouped according to their major degradative end product. Some amino acids are listed more than once because different parts of their carbon skeletons are degraded to different end products. The figure shows the most important catabolic pathways in vertebrates, but there are minor variations among vertebrate species. Threonine, for instance, is degraded via at least two different pathways, and the importance of a given pathway can vary with the organism and its metabolic conditions. The glucogenic and ketogenic amino acids are also delineated in the figure, by color shading. Notice that five of the amino acids are both glucogenic and ketogenic. The amino acids degraded to pyruvate are also potentially ketogenic. Only two amino acids, leucine and lysine, are exclusively ketogenic.

In rodents

High Diet models

High fat-diet (60-70 %) / high carbohydrates (chow) / cafeteria diet

Genetic models

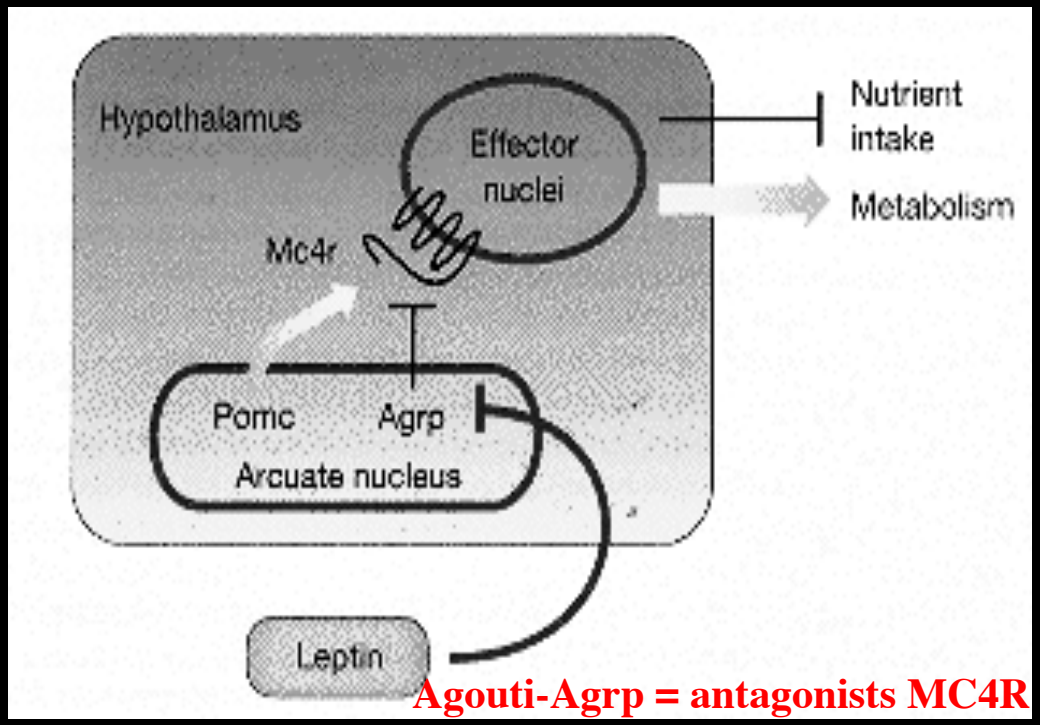
GTG obese mice : GoldThioGlucose toxic for hypothalamus---> hyperphagia

***ob/ob* mice :mutation in leptin gene/X 6 / hyperphagia (stay leptin sensitive)**

***db/db* mice : mutation in the leptin receptor (leptin resistant)**

^{y}A : Agouti protein ectopic expression mice ---> hyperphagia (regulated by leptin)

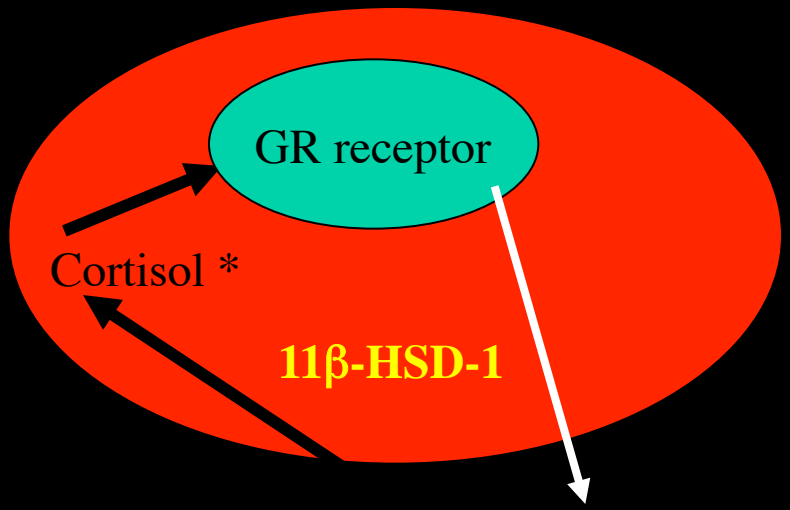
MC4R -/- : mutations in 3-5 % found in patients (BMI > 40)



Agouti-Agrp = antagonists MC4R

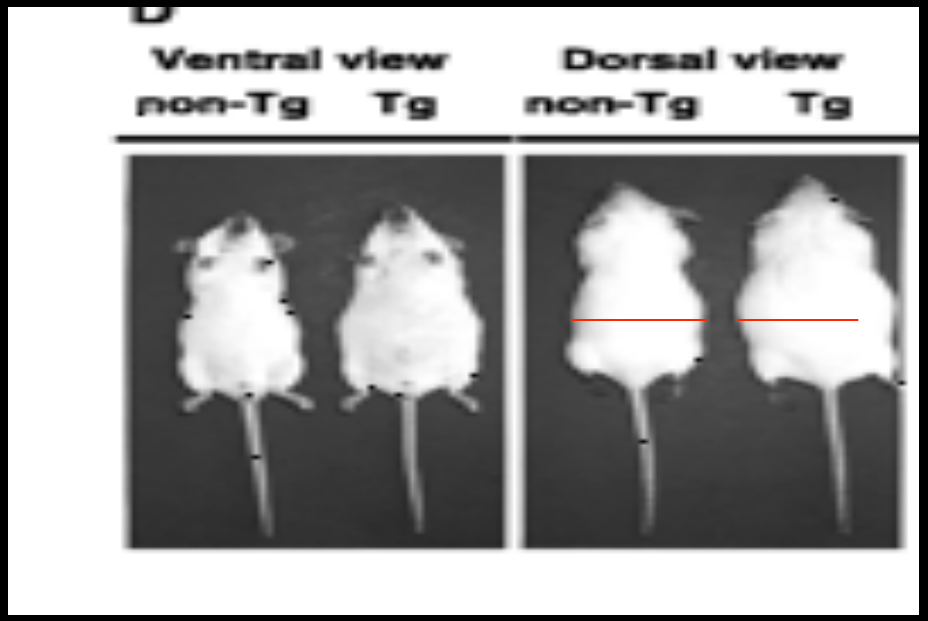
- promoter of the human AGRP and multiple regulatory elements, including two TATA boxes, one CCAAT box, and three CACCC boxes.
- two sites for the STAT transactivators.
- a polymorphism, A67T was identified in the third exon of the gene but it was not associated with obesity or type 2 diabetes clinical profiles.

Excess of glucocorticoids produce visceral obesity and diabetes, but circulating glucocorticoid levels are normal in obese patients *(Mazuzaki et al., Science 2001)*



Adrenal ---> cortisol *---> cortisone

Visceral obesity



Glucocorticoids can be produced locally from inactive 11-keto forms through the enzyme 11beta-hydroxysteroid dehydrogenase type-1 (11beta HSD-1). Transgenic mice overexpressing 11beta HSD-1 selectively in adipose tissue to an extent similar to that found in adipose tissue from obese humans.

* increased adipose levels of cortisol
* visceral obesity that was exaggerated by a high-fat diet
* insulin-resistant diabetes
* hyperlipidemia
* hyperphagia despite hyperleptinemia

Increased adipocyte 11beta-HSD-1 activity may be a common molecular etiology for visceral obesity and the metabolic syndrome.