Adipose tissue as an endocrine organ: the role in obesity and type2 diabetes

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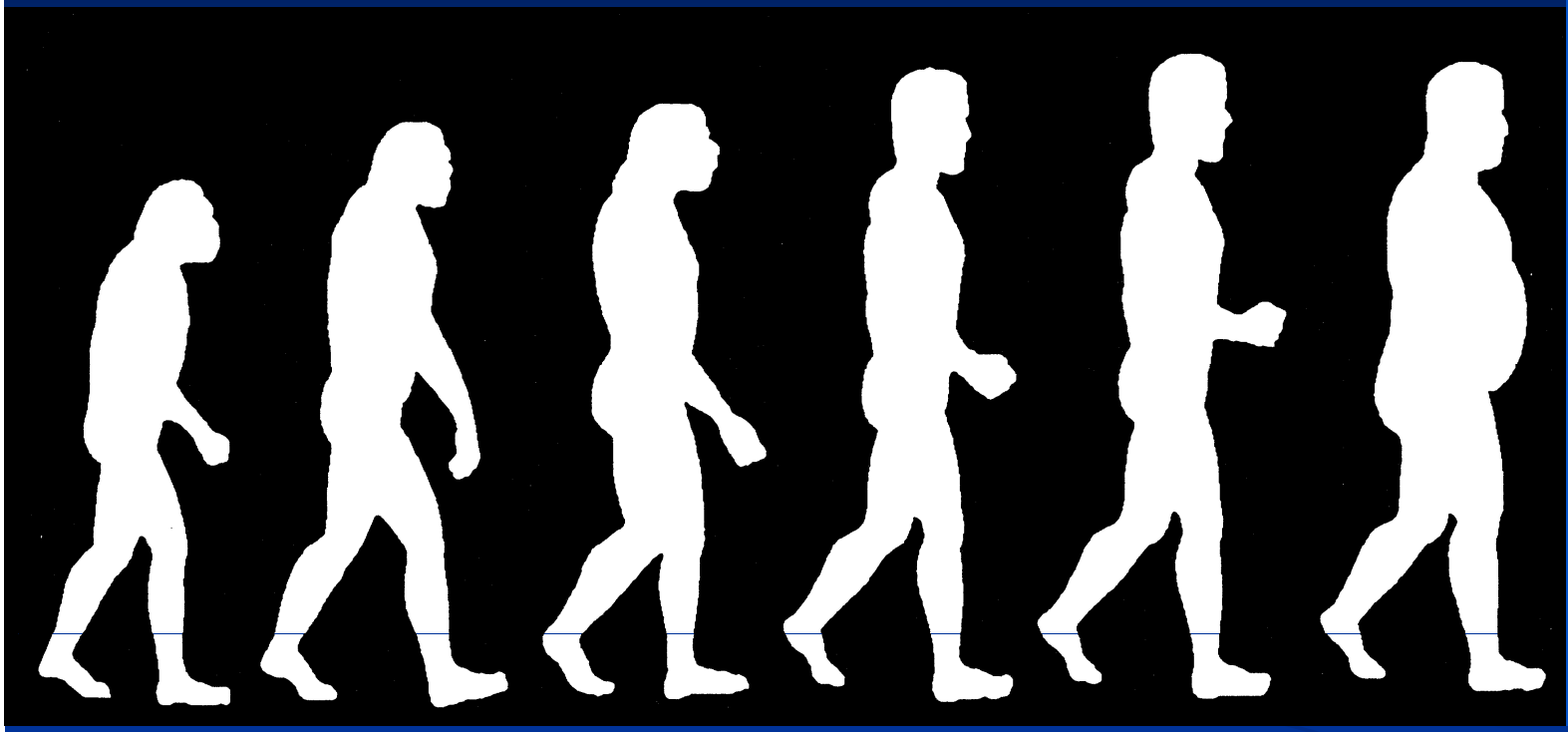
Our prehistorical progenitors clearly did not have the opportunity to suffer either from obesity or anorexia nervosa

Thrifty genes theory – genes predisposing to effective energy storage enabled to survive during times of starvation, however they predispose to obesity nowadays.

Progression of mankind development



2.5 milion years

50 years

….. But in modern societies the thrifty genes are rather harmful than useful

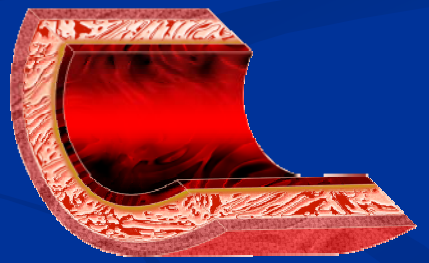
Adapted from R. Unger

Increasing prevalence of obesity represents one of the major problems of current medicine

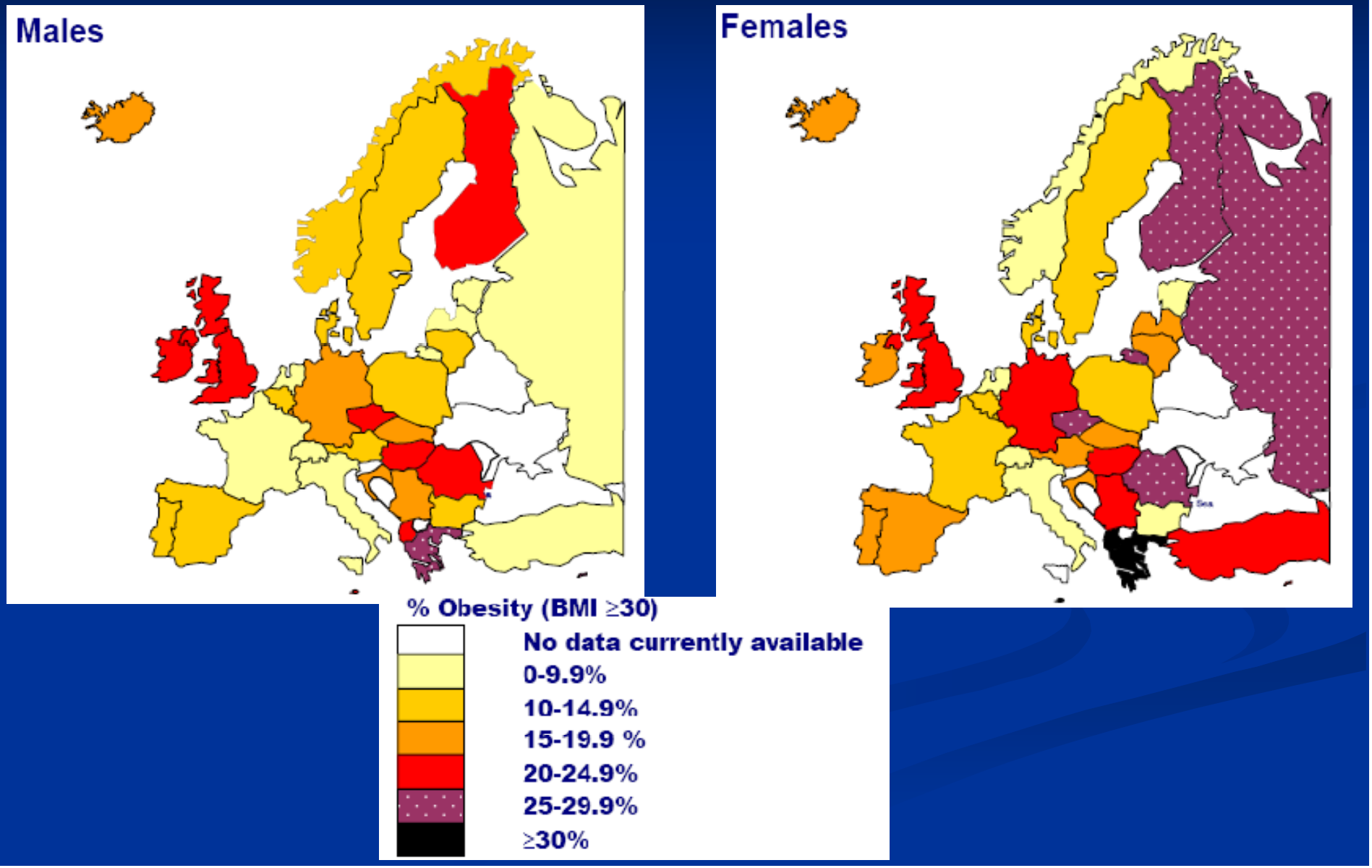
Insulin resistance syndrome

- Obesity
- Arterial hypertension
- Hypercoagulation state
- Insulin rezistance/type 2. diabetes mellitus
- Dyslipidemia

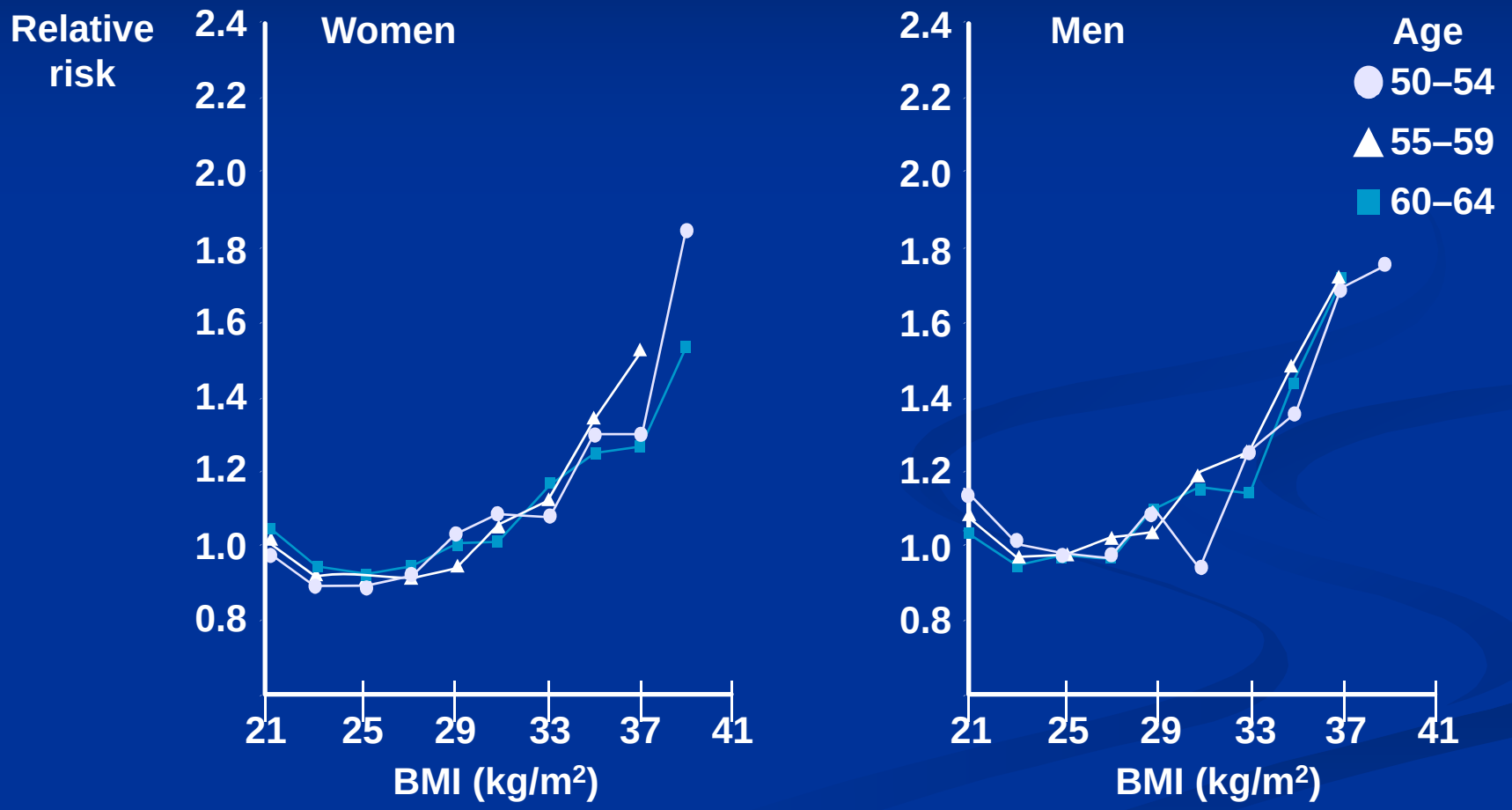
3-fold increased risk of atherosclerosis and its complications (myocardial infarction, Stroke etc.)



Obesity is a major health problem



BMI a mortality



Waaler. Acta Med Scand 1984; 679(Suppl): 1–56

Definition of obesity

Increased fat storage in organism

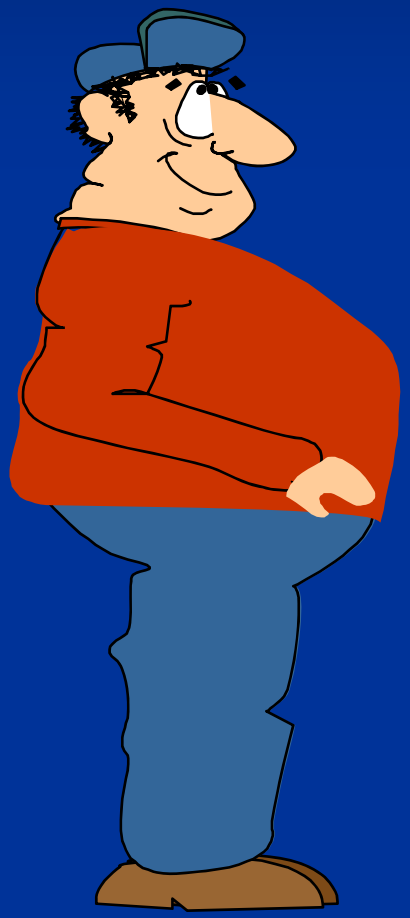
- Normal content of body fat
  - In men less than 15 - 20 %
  - In women less than 25 %

But the body fat measurement is sometimes complicated……

- Clinically useful are
  - anthropometry (skin folds, waist to hip ratio (WHR), SAD)
  - bioimpedancy
  - imaging methods (CT, DEXA, MR, UZ)

In practise supplied by body weight measurement

Obesity is classified by Body Mass Index (BMI)



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

Clasification	BMI (kg/m^2)	Metabolic c.
Normal 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 circumference is a helping indicator of visceral fat – this fat is the most metabolically active and thus the most harmful

Women

>88 cm = highly increased risk[1]
>80 cm = increased risk[1]

Men

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

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

„Simple“ obesity

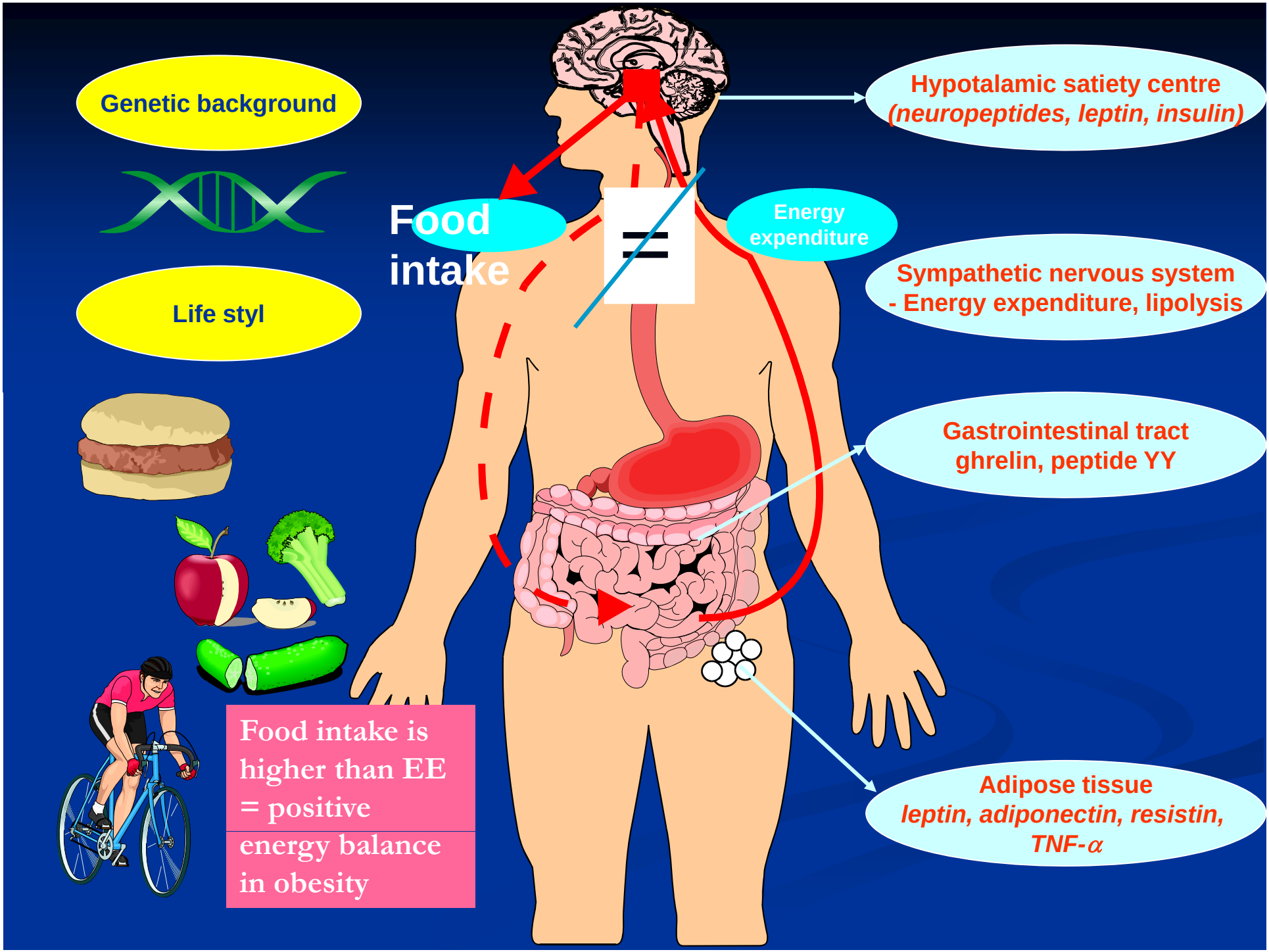
Multifactorial

metabolic disease

with genetically-determined tendency to

the accumulation of fat storage

during positive energy balance


Genetic background
Life styl
Food intake
=
Energy expenditure
Hypotalamic satiety centre
(neuropeptides, leptin, insulin)
Sympathetic nervous system
- Energy expenditure, lipolysis
Gastrointestinal tract
ghrelin, peptide YY
Adipose tissue
leptin, adiponectin, resistin, TNF-α
Food intake is higher than EE = positive energy balance in obesity


Fit fat vs. unfit fat – it is better to be obese sportsman than lean unsportsman
Obese sportsmen are of significantly lower cardiovascular complications than obese unsportmen of equal BMI

Why obesity leads to severe health complications?

The basis of the obesity dangerness is its close connection with other parts of metabolic syndrome

The presence of metabolic syndrome significantly increases mortality and morbidity on cardiovascular diseases

Insulin resistance syndrome (Syndrome X, Metabolic Syndrome, Deadly quartet, Secret killer)

Group of clinical manifestations and biochemical abnormalities that increases the risk of atherosclerosis and associated complications (heart failure, cerebral apoplexy, ischemic disease atc.) – primary abnormality leading to other complications is insulin resistance, important part is obesity of visceral type (apple type)

Revised definition of Metabolic Syndrome (Reaven, 1993)

- **Primary abnormality is insulin resistance**
- Most tightly related complications are hypertension, hypertriglyceridemia and diabetes/altered glucose tolerance
- Less tighly related are alterations in coagulation and fibrinolysis
- More less related are ischemic heart disease and android obesity

The new International Diabetes Federation (IDF) definition of MS

Central obesity *(defined as waist circumference* ≥ 94cm for Europid men and ≥ 80cm for Europid women, *with ethnicity specific values for other groups)*

plus any two of the following four factors:

- ***raised TG level:*** ≥ 150 mg/dL (1.7 mmol/L), *or* ***specific treatment for this lipid abnormality***
- ***reduced HDL cholesterol***: < 40 mg/dL (1.03 mmol/L*) in males and < 50 mg/dL (1.29 mmol/L*) in females, ***or specific treatment for this lipid abnormality***
- ***raised blood pressure:*** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, ***or treatment of previously diagnosed hypertension***
- ***raised fasting plasma glucose*** (FPG) ≥ 100 mg/dL (5.6 mmol/L), ***or previously diagnosed type 2 diabetes***
  If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Additional metabolic criteria for MS in research

Abnormal body fat distribution	General body fat distribution (DXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidaemia (beyond elevated triglyceride and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycaemia	OGTT
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Proinflammatory state	Elevated high sensitivity C-reactive protein (SAA) Elevated inflammatory cytokines (eg TNF-alpha, IL-6) Decrease in adiponectin plasma levels
Prothrombotic state	Fibrinolytic factors (PAI-1 etc) Clotting factors (fibrinogen etc)
Hormonal factors	Pituitary-adrenal axis

Why does SIR initiate?

- ≤ 50 % genetic background
- The rest environmental and other factors

Heredity is polygenic – disruption is determined from tens to hundreds genes – the resolution is not the gene therapy

Why is SIR dangerous?

- 3-times higher risk – 2type DM, hyperlipidemia, lung disease, sleeping apnoe syndrome
- 2-3 times higher risk - ICHS, hyperurikemia, joint disease
- 2-times higher risk – postmenopausal breast cancer, endometrial and intestinal tumours, infertility

Definition of insulin resistance

Conditions when physiological level of insulin evokes subphysiological (insufficient) biological effect.

Main effects of insulin in humans:

- Stimulation of glucose uptake by peripheral tissues and its metabolism and storage in a form of glycogen and fat
- Reduction of glycogenolysis and de novo glucogenesis in liver
- Reduction of these effects leads to hyperglycemia (but IR does not influnce antilypolitic effects of insulin)

Obesity is always accompanied by some degree of insulin resistance

IR is defined as a smaller than expected biological response to a given dose of insulin.

Insulin resistance is a principal component of Insulin resistance syndrome:

-Obesity
-Insulin resistance/diabetes
-Dyslipidemia
-Arterial hypertension
-…

The presence of Insulin resistance syndrome markedly increases cardiovascular morbidity and mortality.

Causes a consequences of insulin resistance

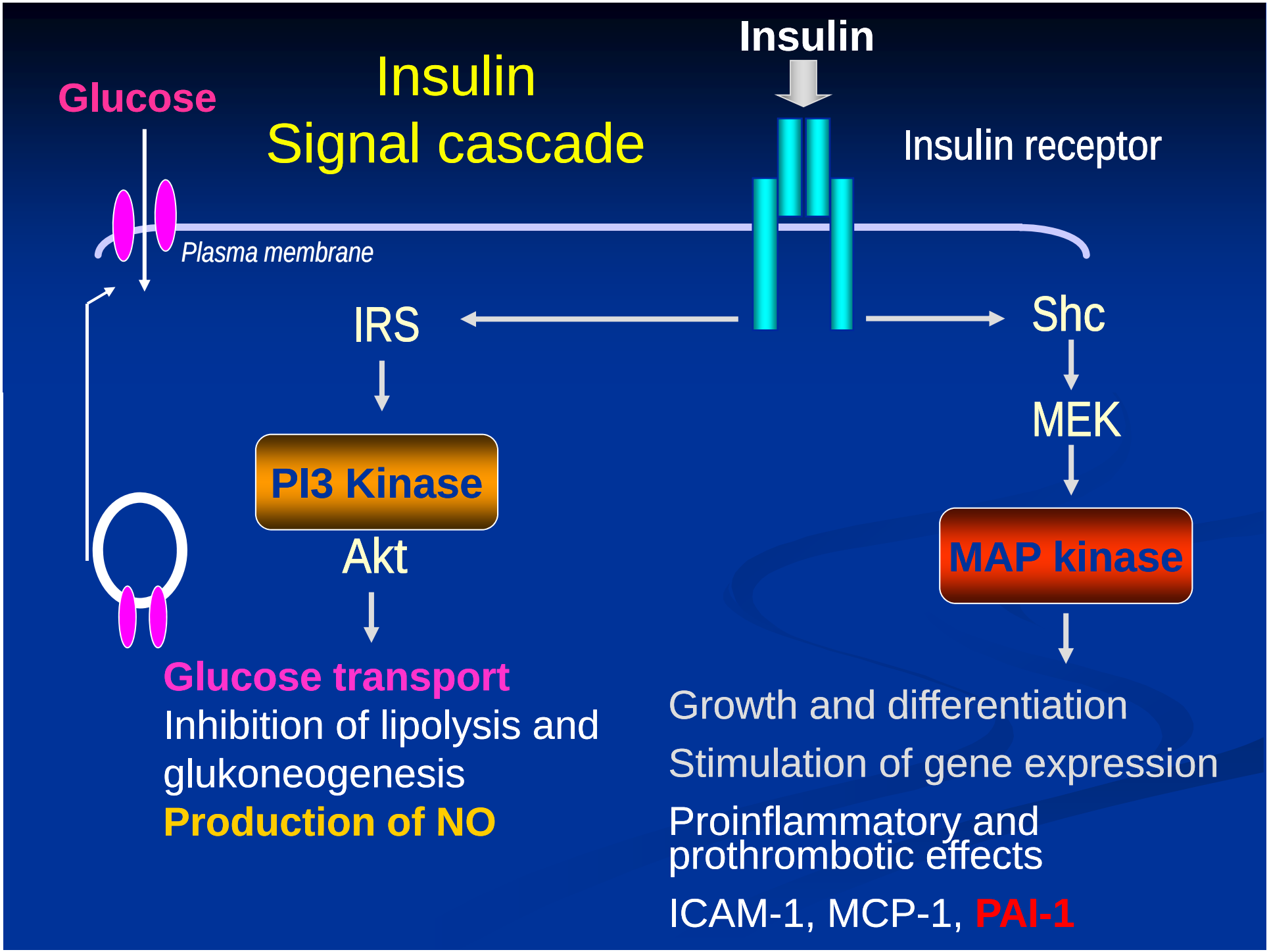
Cause is reduced sensitivity of peripheral tissues (liver, muscle, adipose tissue) on effects of insulin

Consequence is compensatory increase of insulin secretion that shortly compensates insulinoresistance, but leads to its worsening in a long-lasting manner.

⇒ after depletion of secretory storage of pancreas relative insufficence of insulin occurs and 2 type Diabetes mellitus develops

Mechanism of development of insulin resistance

- Mutation of gene for insulin receptor
- antibodies against insulin receptor
- Decrease number of insulin receptors during hyperinsulinemia
- **Defect(s) on the level of postreceptor signal cascade of insulin receptor – most common in obese subjects**


Insulin
Glucose
Insulin
Signal cascade
Insulin receptor
Plasma membrane
IRS
Shc
MEK
PI3 Kinase
Akt
MAP kinase
Glucose transport
Inhibition of lipolysis and
glukoneogenesis
Production of NO
Growth and differentiation
Stimulation of gene expression
Proinflammatory and
prothrombotic effects
ICAM-1, MCP-1, PAI-1

Adipose tissue in obesity

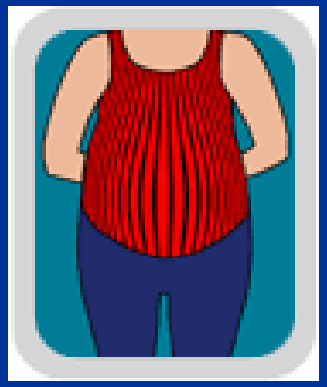
The role of adipose tissue in human body

- Adipose tissue constitutes about 20-30 % of total body mass
- Source of energy (long-term starvation induces triglyceride breakdown to fatty acids and glycerol, both is further used as an energy source)
- Thermoregulatory function (thermic isolator)
- Mechanical protection of internal organs
- Endocrine function (control of food intake, lipid and carbohydrate metabolism)
- Accumulation of lipophyllic compounds (exogenous toxins)
- Conversion of prohormones to active hormones (increased local production of cortisol in visceral adipose tissue)
- Adipocyte capacity to differentiate and to store lipids is a principal determinant of protection against insulin resistance induced by ectopic fat storage

All adipose tissue is not the same

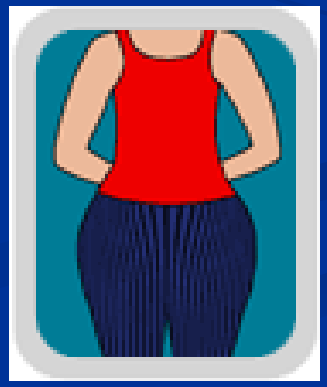
Visceral adipose tissue

- Only ~ 20% of total body fat
- Smaller adipocytes
- More metabolically active
- Direct access of biochemical and hormonal products to the liver
- Closer correlation with metabolic complications of obesity



Subcutaneous adipose tissue

- Quantitatively predominant adipose tissue depot
- Larger adipocytes relative to visceral
- Less metabolically active
- Correlation with metabolic complications of obesity is still present but is weaker than that of visceral fat

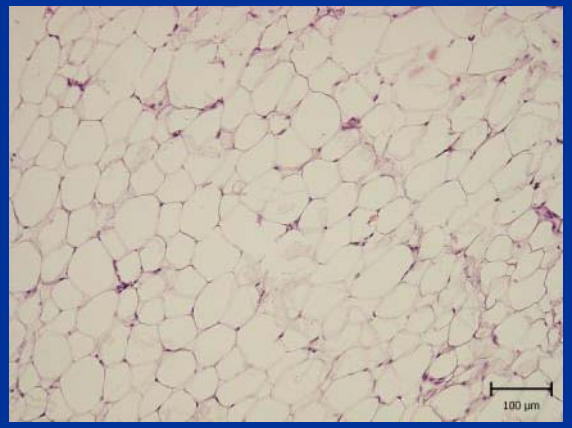


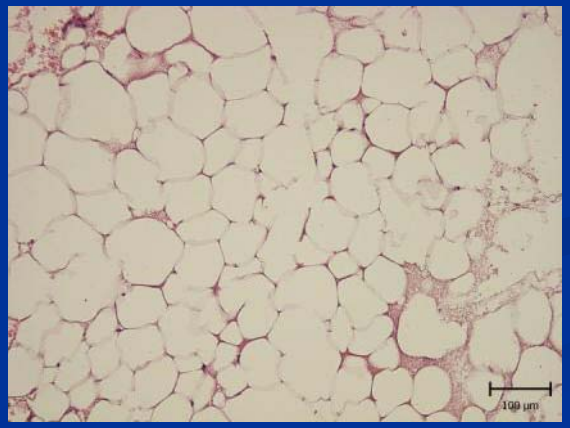
The size of adipocytes closely correlates with its metabolic features

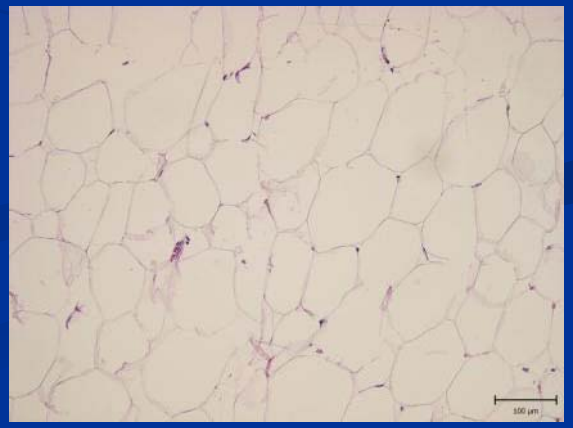
Malnutrition
(Anorexia nervosa)

Normal
(sligthly overweight)

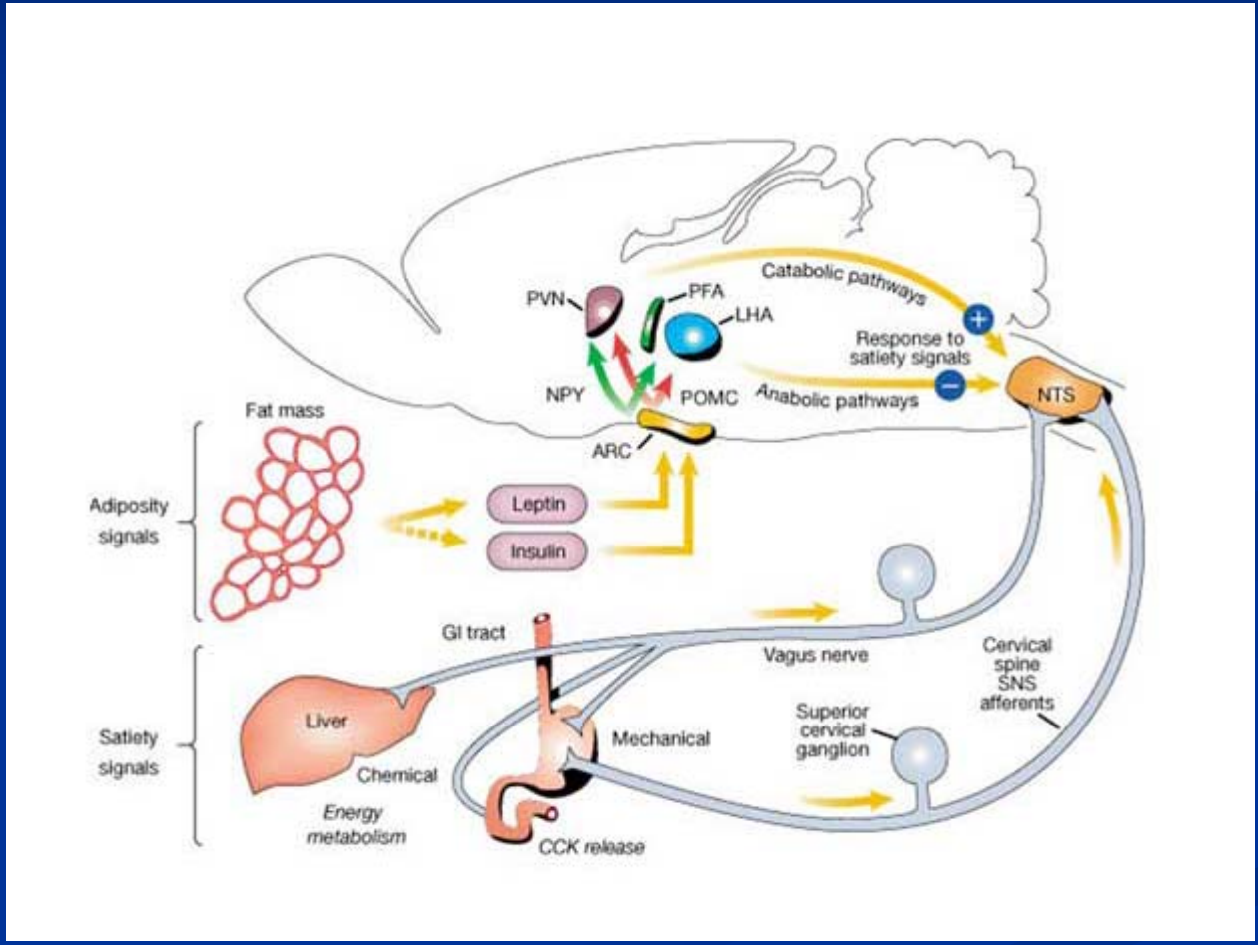
Obese







Adipose tissue plays an important role in the regulation of energy homeostasis



Products of adipose tissue

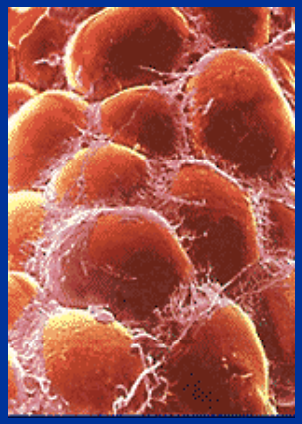
FFA, glycerol

Adipocyte secreted cytokines (leptin, adiponectin, visfatin, acylation stimulating protein, metallothionein I, II, nerve growth factor, haptoglobin

Chemokines – MCP-1, IL-8, Eotaxin, CCL-5

Stromovascular and adipocyte-secreted cytokines – IL-6, TNF-α, IL-1β

Growth factors – FGF, TGF-β, CNTF, MCSF



Hemostatic factors – PAI-1, Tissue factor

Extracellular matrix proteins – collagen type III, fibronectin

Adhesion molecules – VCAM-1, ICAM-1

RAS components – renin, angiotensinogen, angiotensin I, II

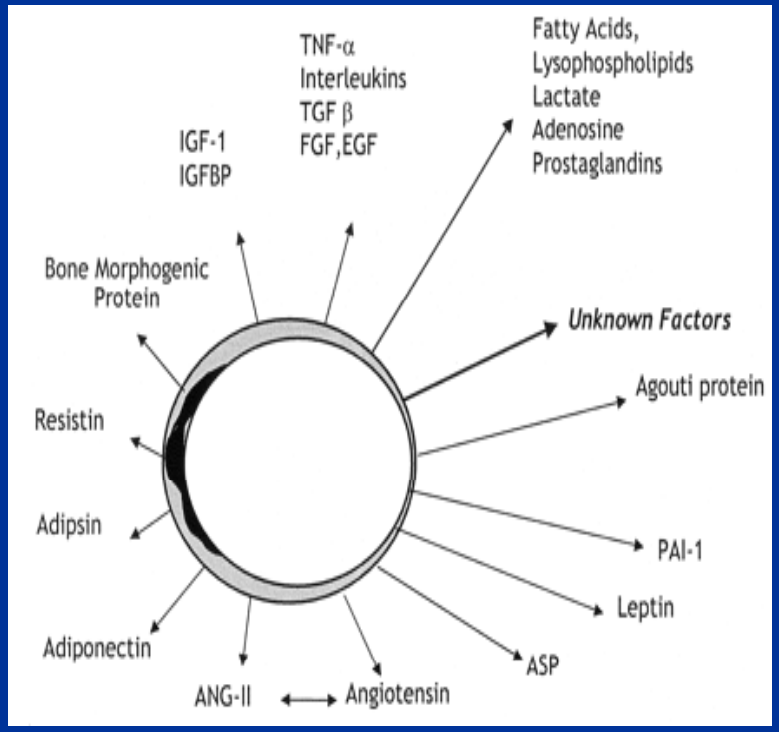
Other factors – resistin, RBP-4, vaspin, omentin, apelin, prolactin

Enzymes – lipoprotein lipase, adipsin, matrix metalloproteinases

Angiogenic factors – VEGF, HGF

Adipose tissue produces numerous hormones and cytokines

These factors are produced not only by adipocytes, but also by macrophages, fibroblasts, endothelial cells and other cells present in adipose tissue

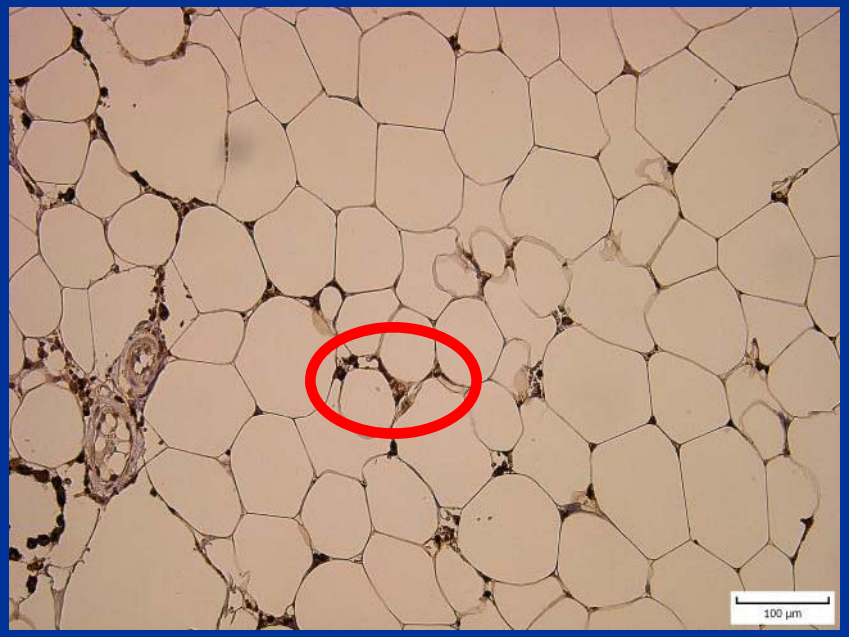


Adipose tissue- derived hormones:

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

These hormones markedly contribute to metabolic regulations

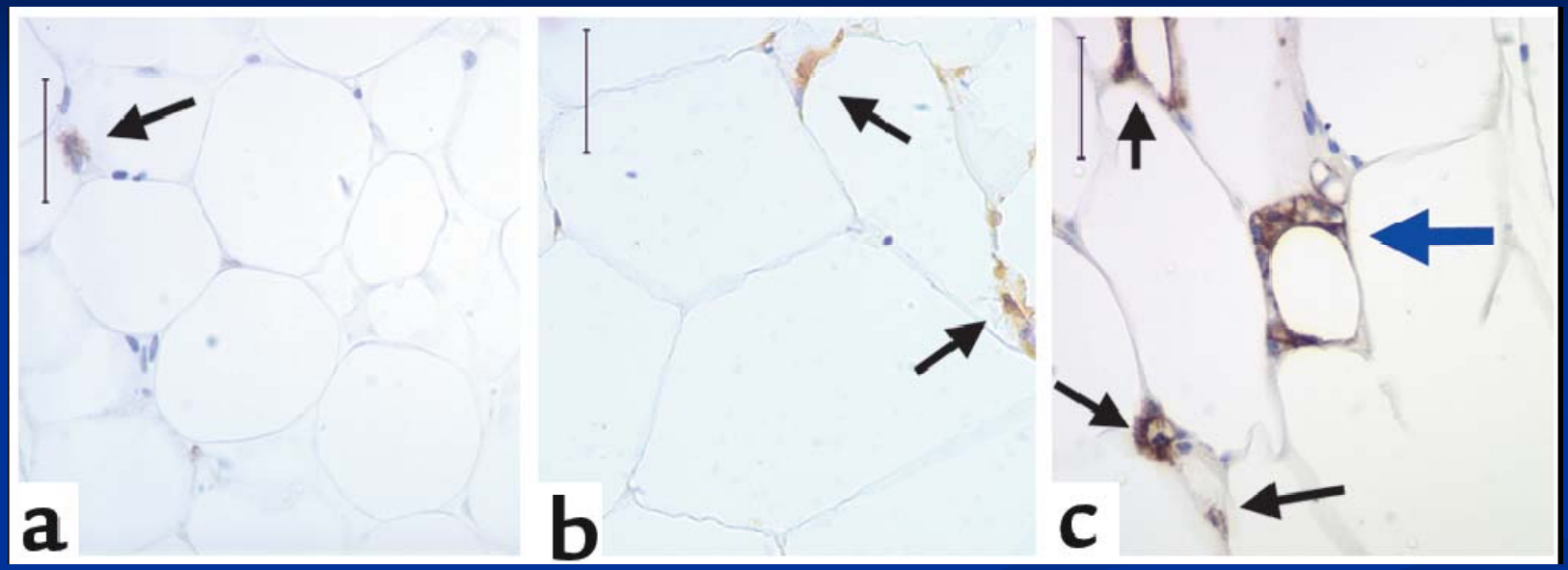
Hormonal production of adipose tissue is not limited to adipocytes. Other cells residing in fat contribute (immunocompetent cells, endothelial cells etc.)



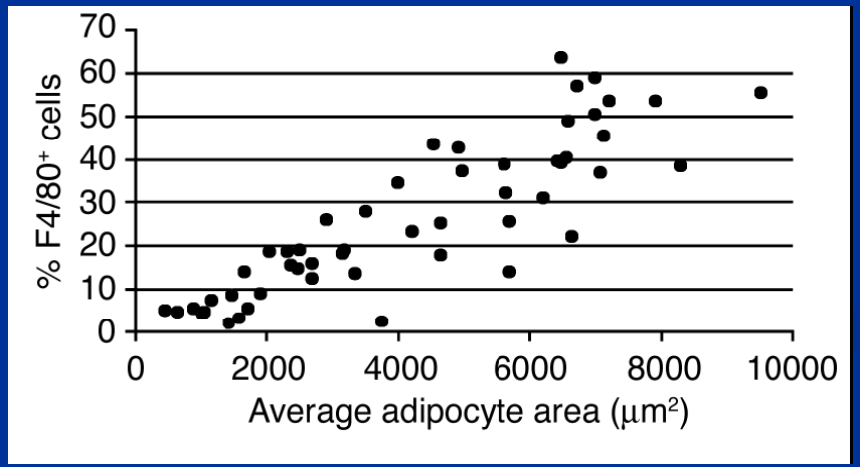
Mayers Hematoxyllin staining
CD68 antibody – immunocompetent cells marker

Van Gieson staining

Obesity leads to subclinical inflammation in adipose tissue



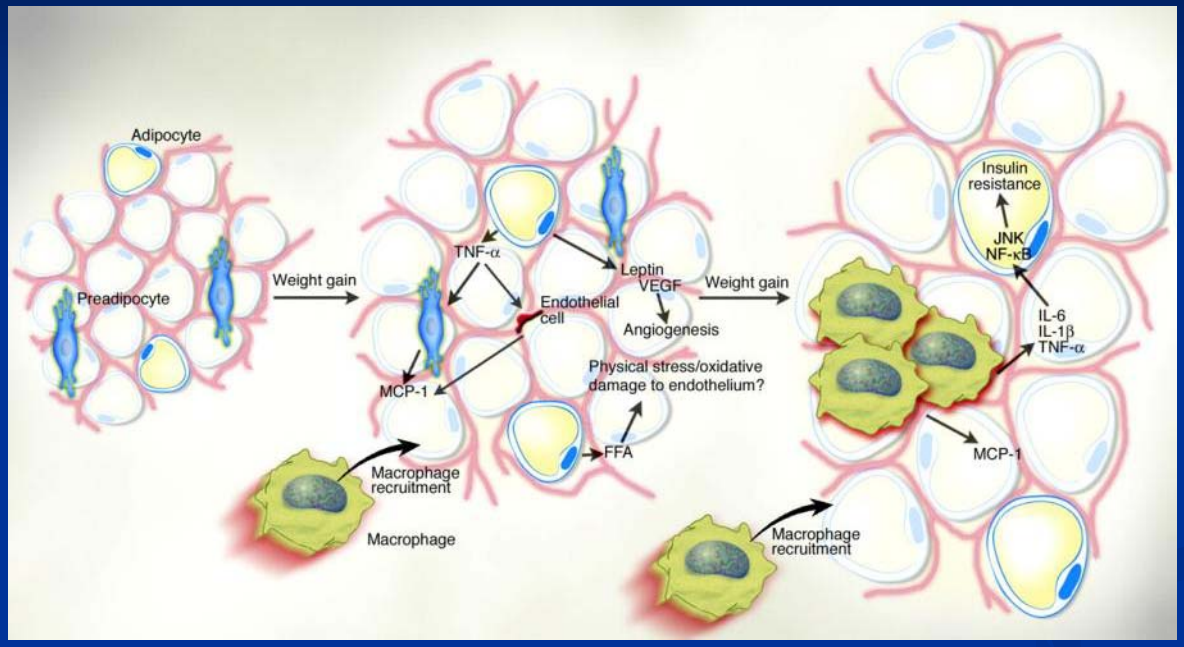
Lean mice Moderately obese mice Morbidly obese mice

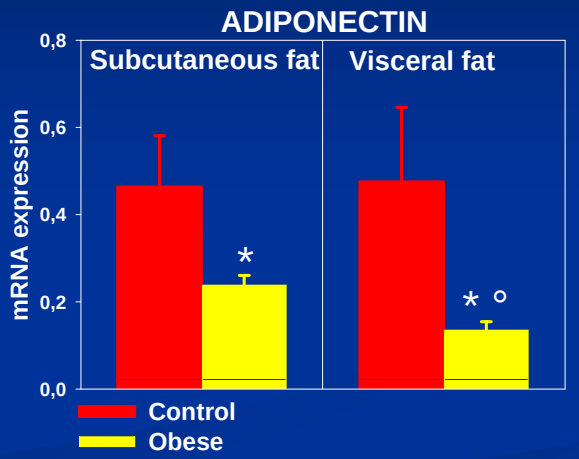


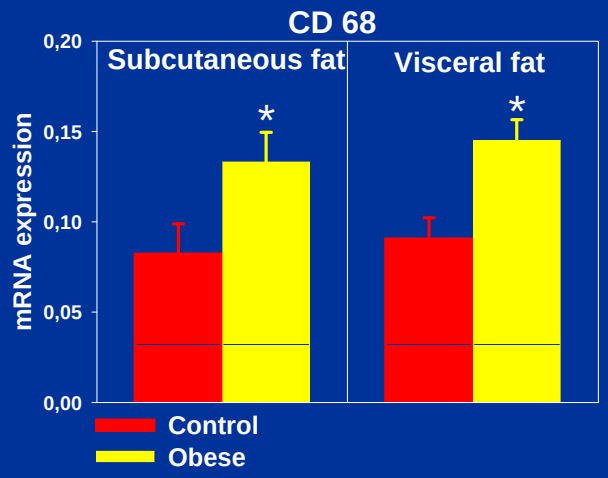
Strong positive correlation between adipocyte size and the number of macrophages in adipose tissue

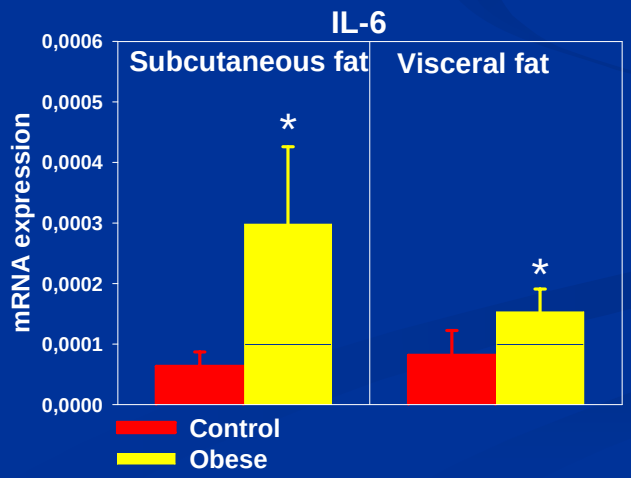
Weisberg et al., JCI, 112:1796–1808 (2003).

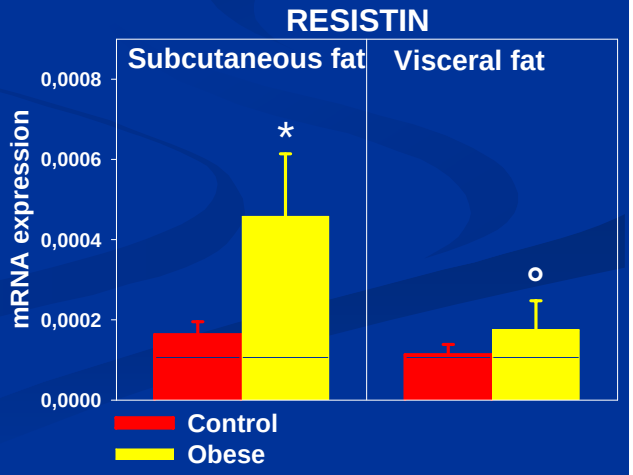
Obesity is accompanied by local inflammatory response in adipose tissue







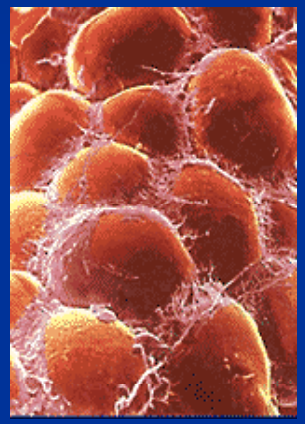




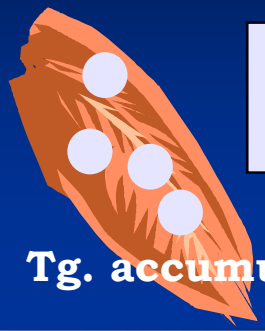
The role of adipose tissue in the etiopathoegensis of insulin resistance

FAT

↑ Lipolysis- ↑FFA

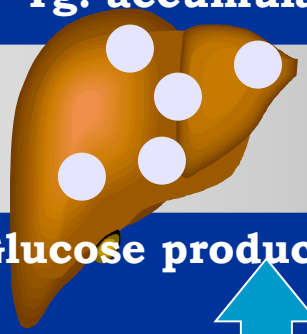


↓ Glucose uptake



INSULIN RESISTANCE

Tg. accumulation



Tg. accumulation

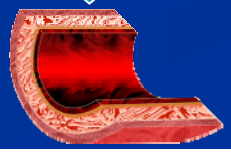
Hyperglycemia

DM 2

↑ Glucose production

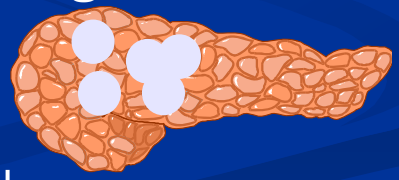
HYPERINSULINEMIA

Endocrine Dysfunction
↑Resistin, TNF-α
↓Adiponectin
Subclinical inflammation



VLDL TG
Hyper ApoB
SD LDL
Atherosclerosis

Tg. accumulation



↓ Inzulin secretion
β-cell destruction

Obesity – „obese“ (hypertrophic) adipocyte

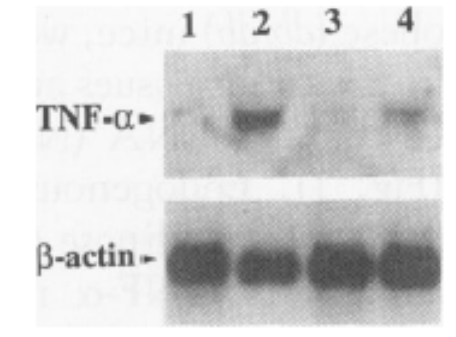
- **“Obese” adipocyte has very low capacity for further storage of triglycerides ⇒ ectopic fat storage (muscle, liver, pancreas)**
- **Release of more free fatty acids leading to insulin resistance**
- **Produces low amount of hormones decreasing insulin resistance (adiponectin) and/or overproduces hormones increasing insulin resistance (rezistin, TNF-α)**

Adipose Expression of Tumor Necrosis Factor–α: Direct Role in Obesity-Linked Insulin Resistance

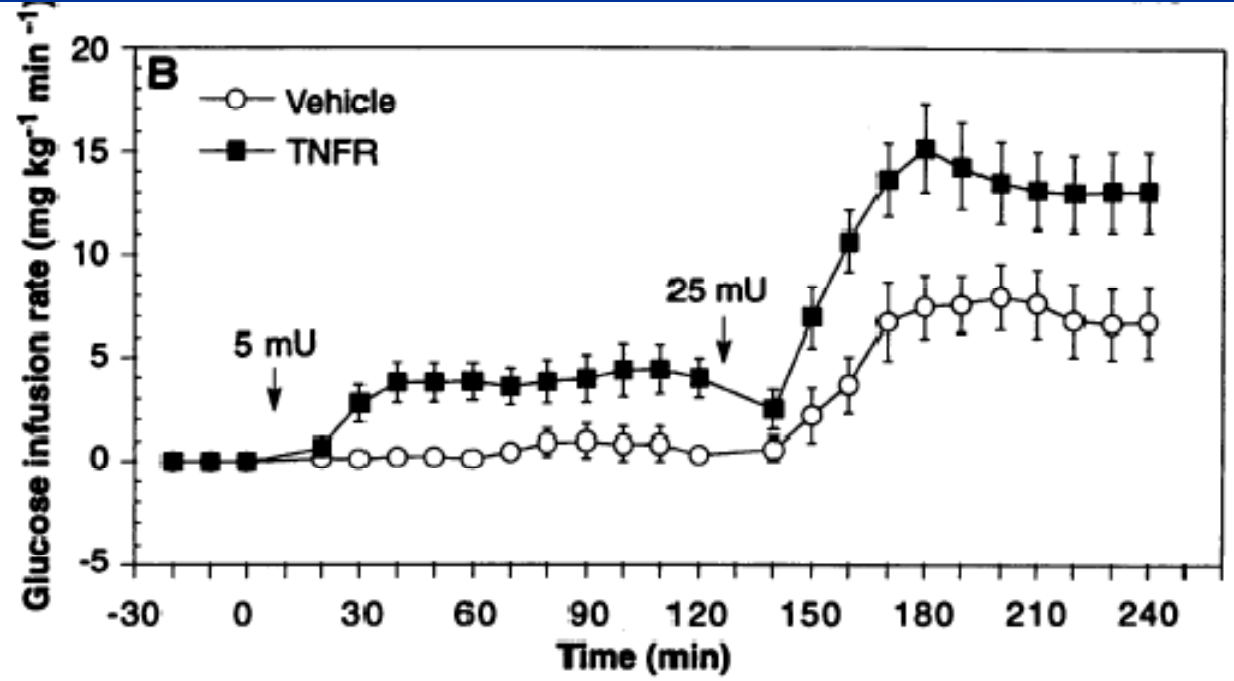
Gökhan S. Hotamisligil, Narinder S. Shargill,
Bruce M. Spiegelman*

SCIENCE • VOL. 259 • 1 JANUARY 1993

TNF-α is abundantly expressed in both adipocytes and stromavascular cells of obese mice

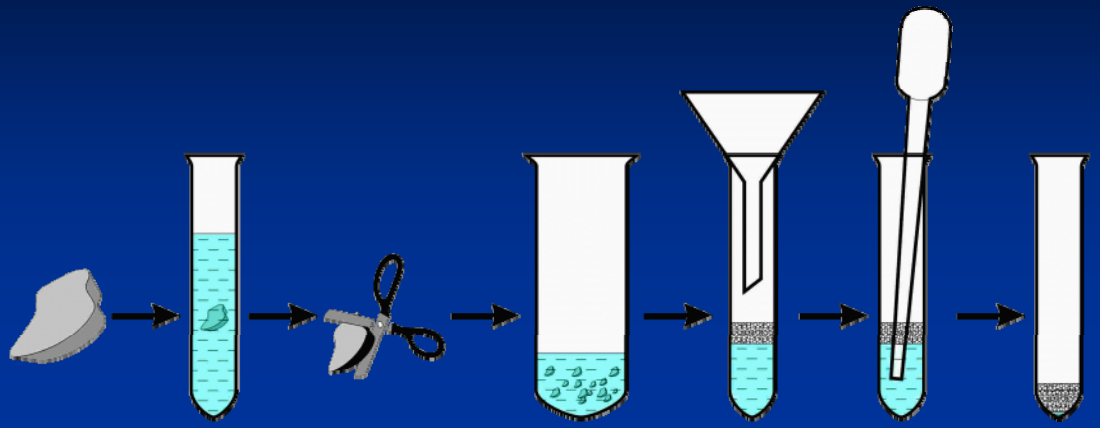


TNF-α neutralization by a recombinant soluble TNF-α receptor IgG chimeric protein improves insulin sensitivity

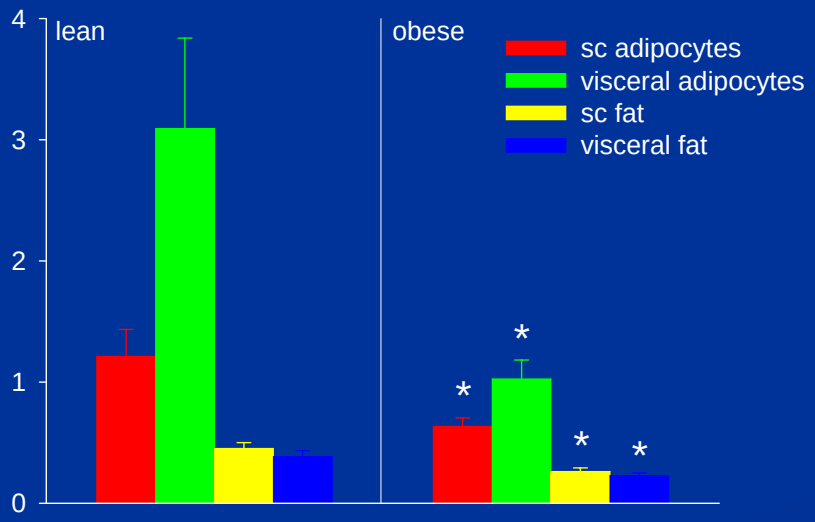


Adipocytes vs. adipose tissue as a source of adipokines

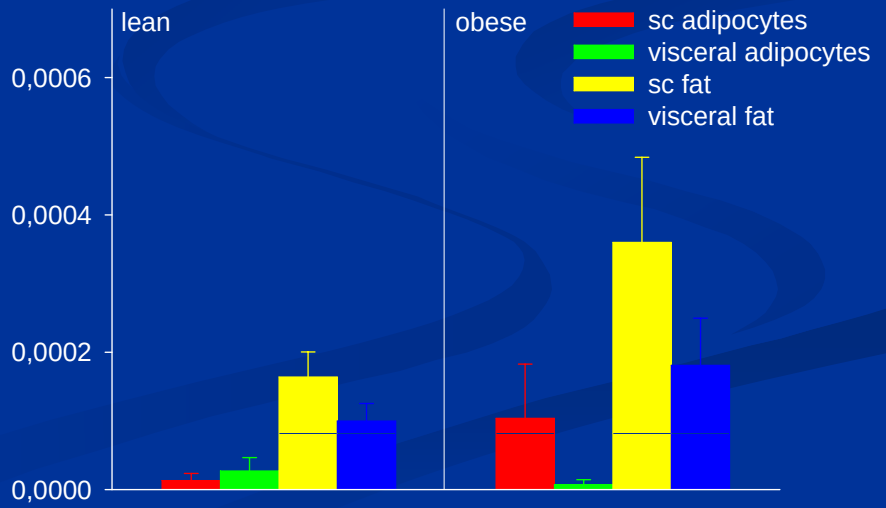
Adipocyte isolation



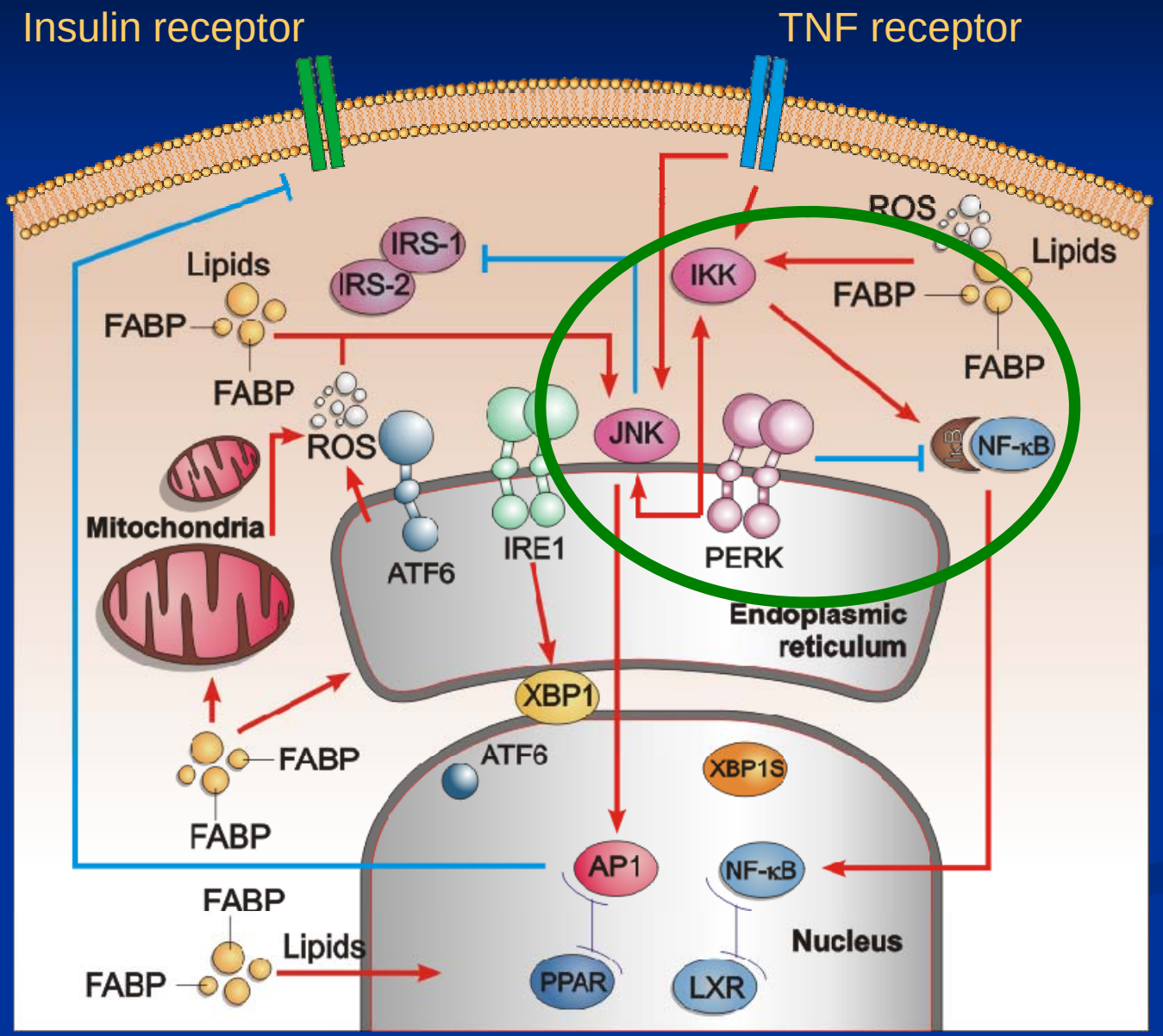
Adiponectin mRNA expression



Resistin mRNA expression

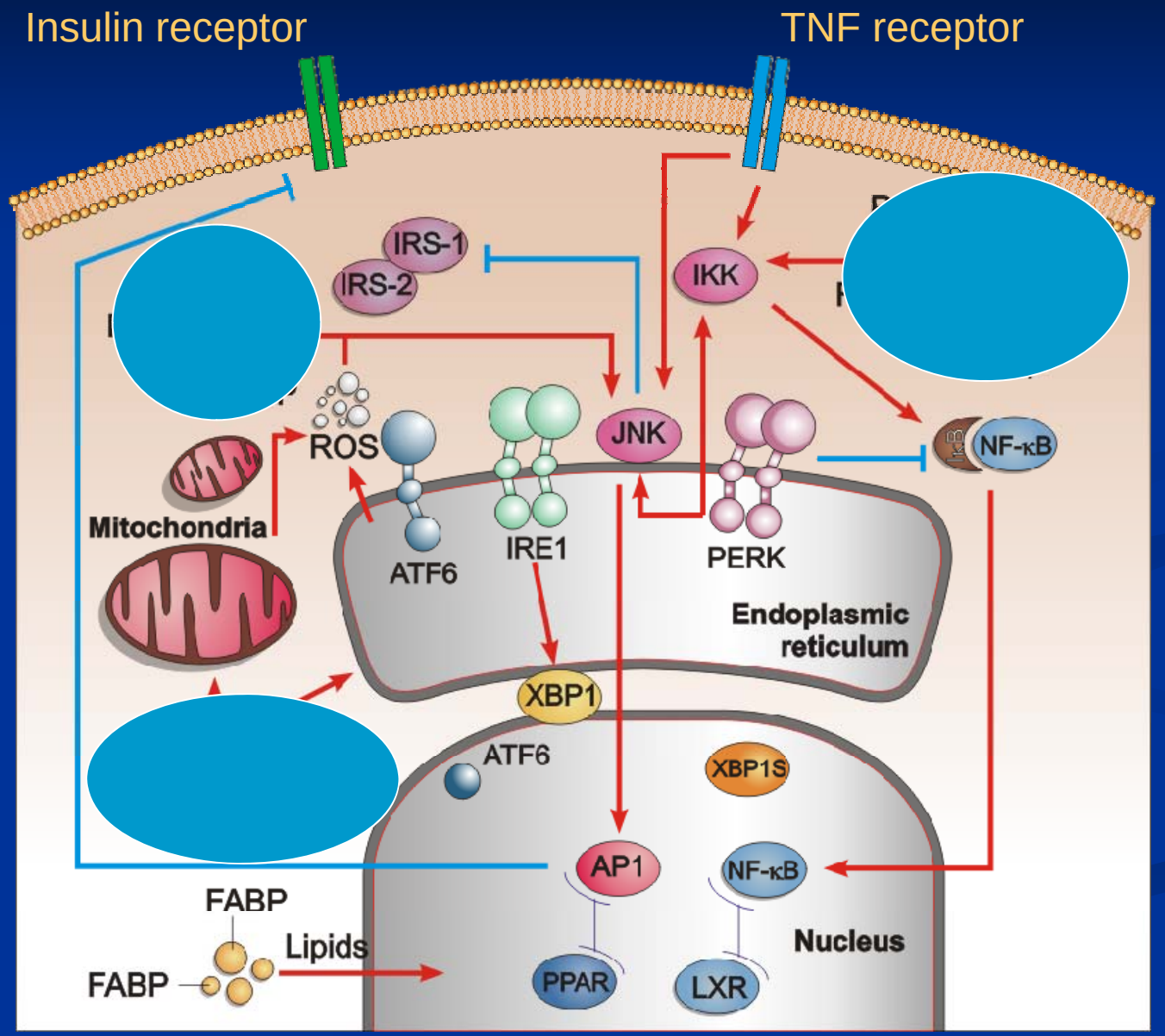


Mechanism of insulin resistance induced by proinflammatory cytokines

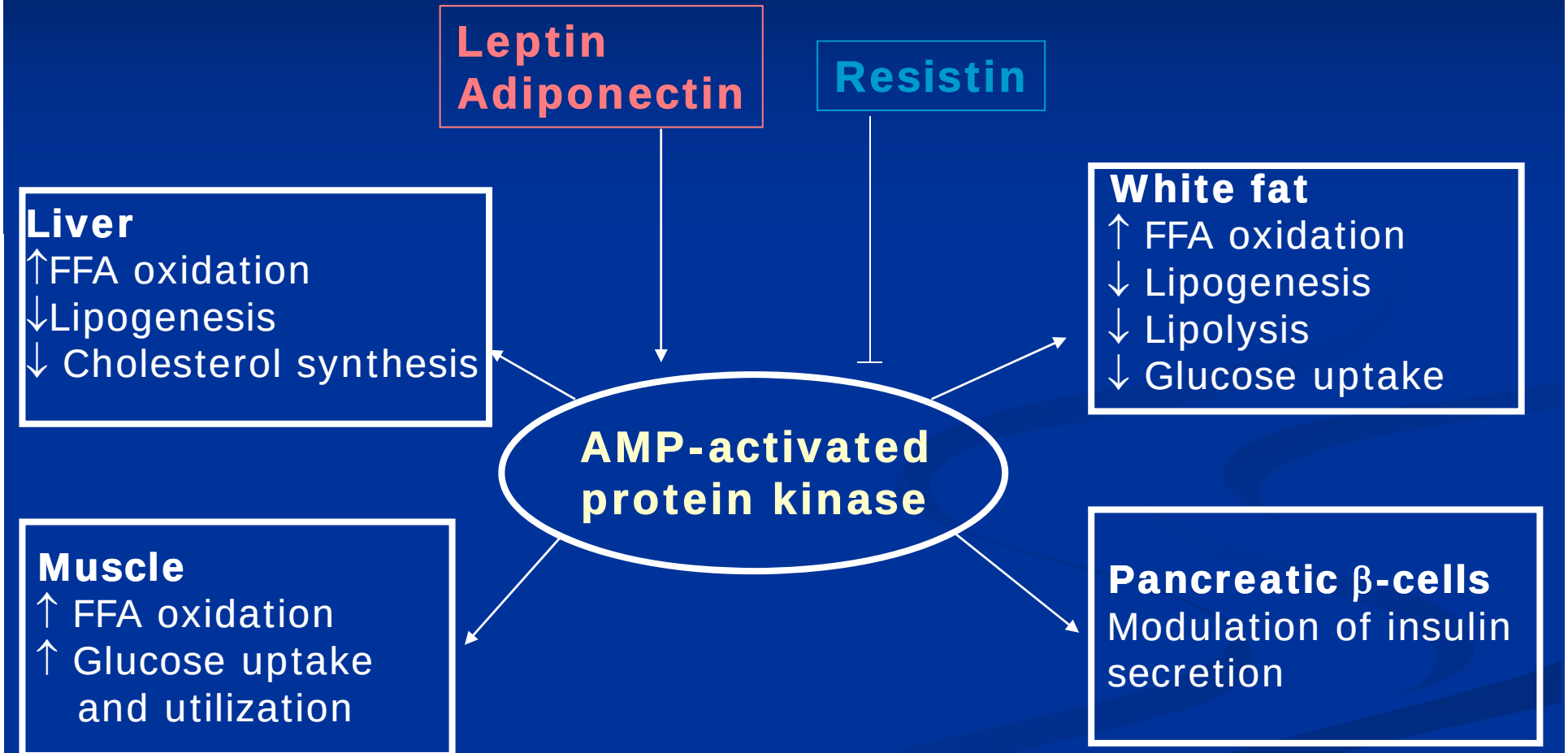


Adapted from Hotamisligil Nature, 2006

Decreased ectopic lipids improve insulin sensitivity



Increased AMP kinase activity as the mechanism of insulin-sensitizing effects of adipokines



Adapted from J. Kopecky

The main cause of the development of insulin resistance is probably „dysfunction“ of adipose tissue

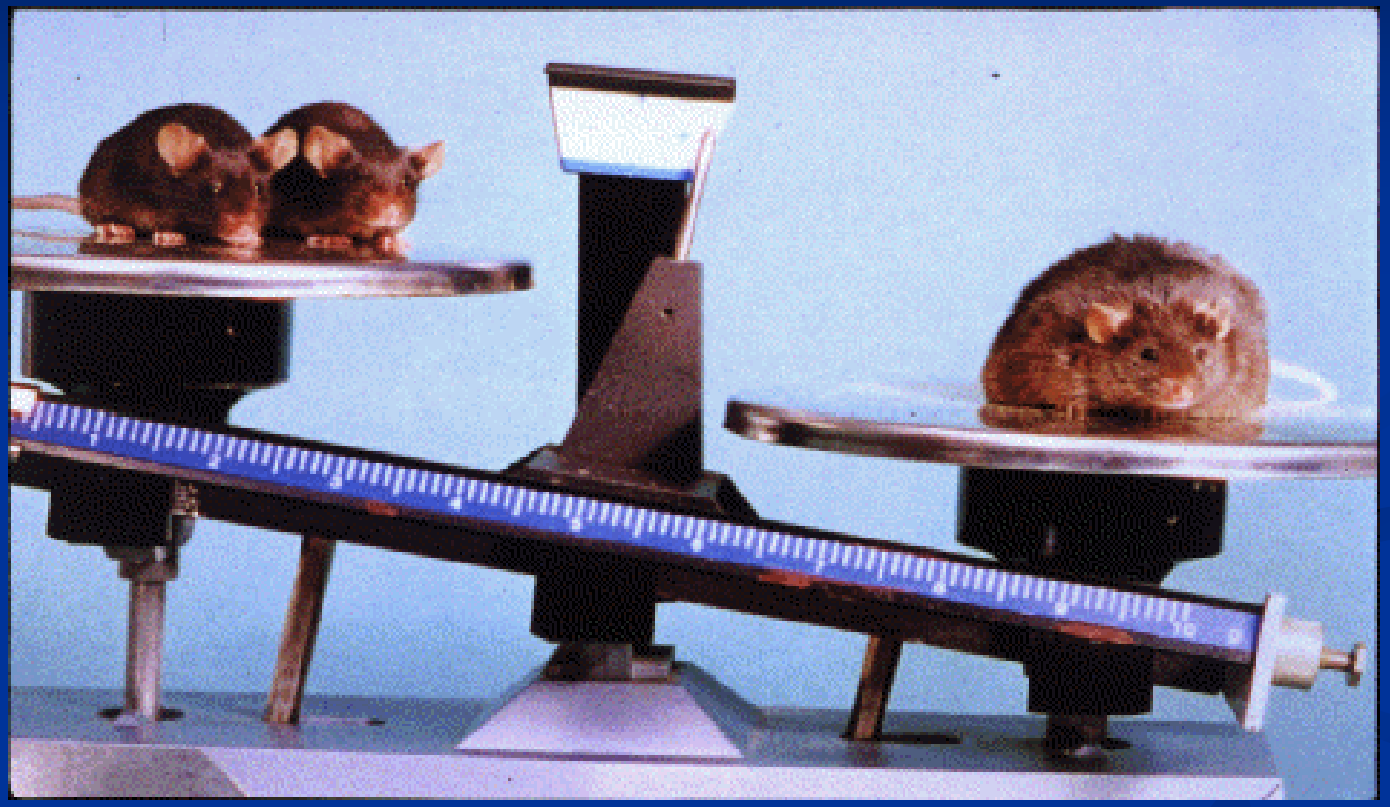
How is the dysfunction of adipose tissue manifested?

- Ectopic fat storage
- Altered production of adipose tissue hormones
- Increased release of free fatty acids with disrupted antilipolytic effect of insulin

Hypothesis of the disturbance of production of adipose tissue hormones

1994 - Adipose tissue can produce hormones

Obese mouse started it all…..

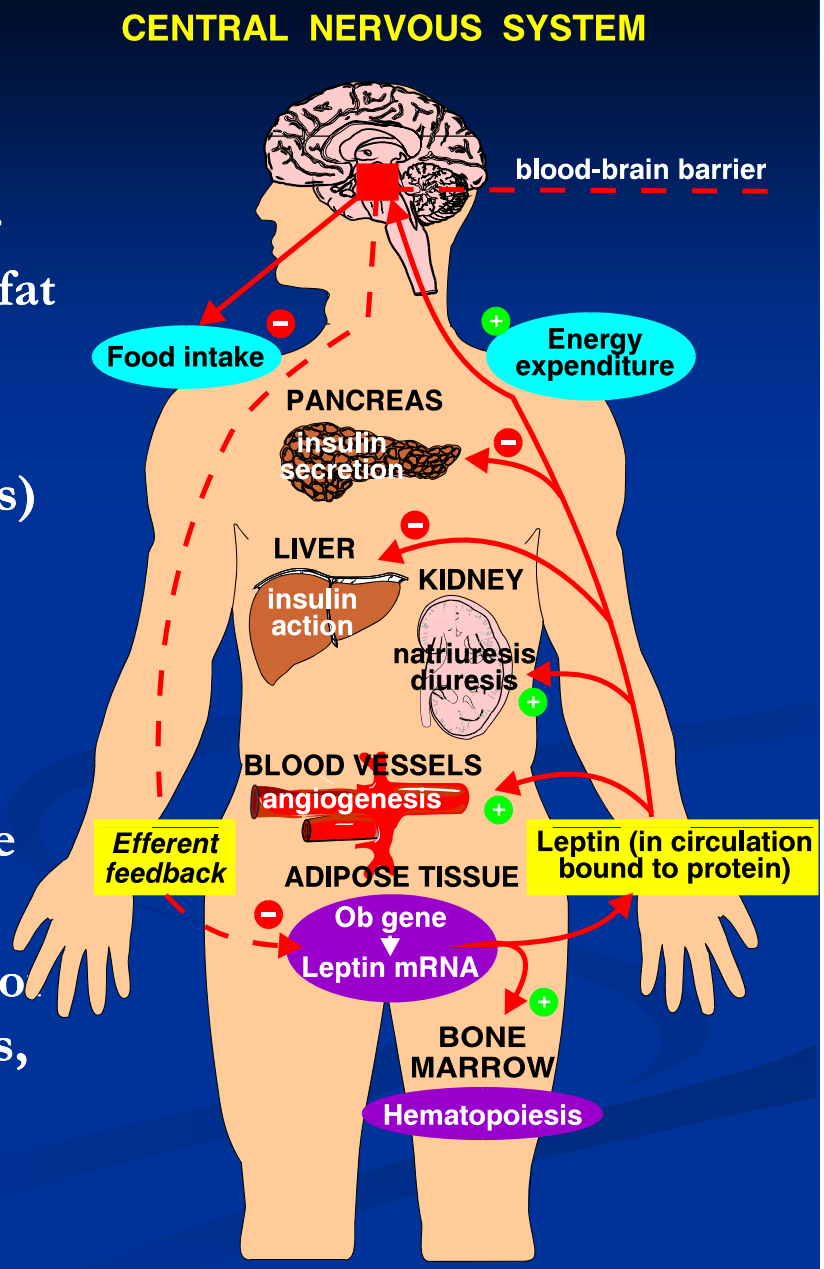


Mutation of *ob* gene encoding protein hormone leptin produced by adipocytes results in morbid obesity in mouse

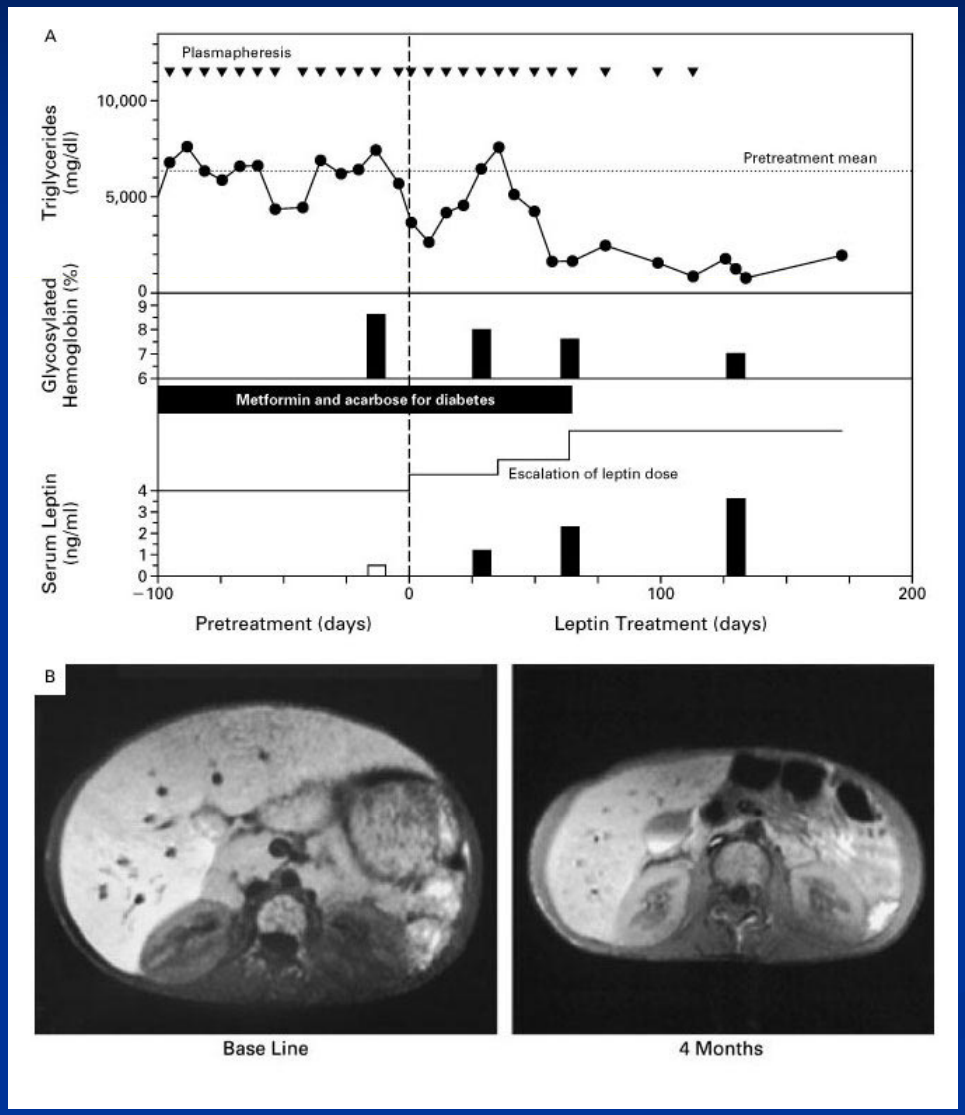
Zhang et al, Nature, 1994.

Leptin

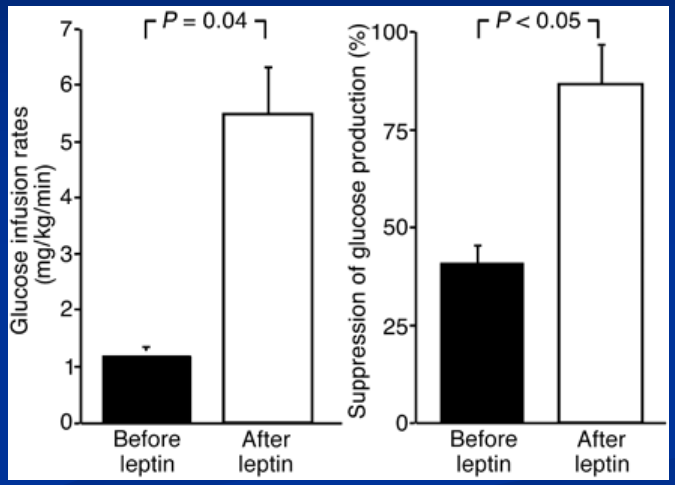
- Pleiotropic protein hormone produced predominantly by adipocytes, its circulating levels usually positively correlate with body fat content
- Regulator of food intake and energy expenditure (central effects in hypothalamus)
- Leptin treatment of leptin-deficient *ob/ob* mice normalized their body weight and recovered their fertility
- Leptin treatment of normal mice induced decrease in body weight (predominantly due to loss of fat)
- Additional possible physiological functions of leptin include the regulation of angiogenesis, blood pressure, hematopoesis etc.



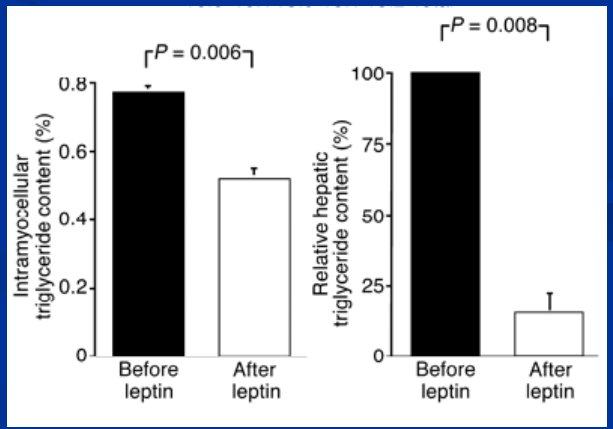
Leptin replacement decreases ectopic fat storage and improves insulin sensitivity in patients with lipodystrophy



Leptin improves insulin sensitivity



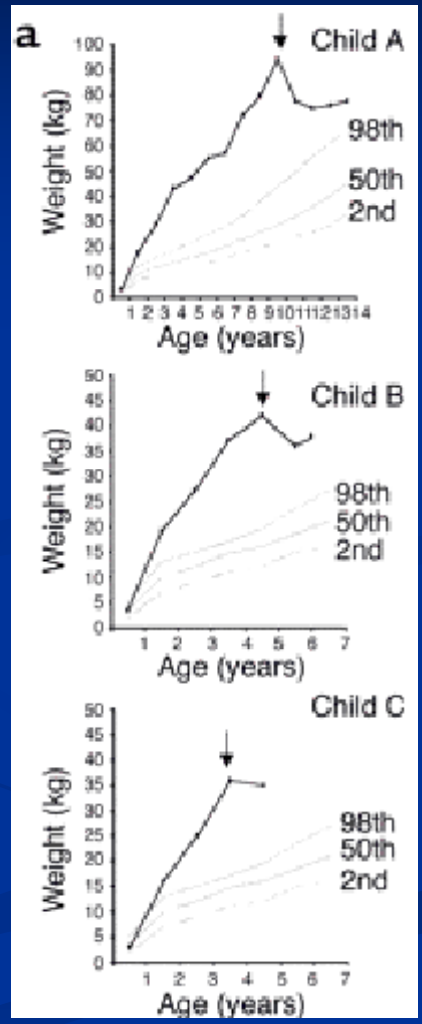
Leptin reduces ectopic fat in liver and muscle



Oral EA, NEJM, 2002; Petersen, KF, JCI, 2002

Mutation of leptin gene in humans leads to morbid obesity

Substitution of leptin Adjusts fenotype



Farooqi SI, *J. Clin. Invest.* **110**:1093-1103 (2002)

Leptin and obesity

- Leptin deficiency is not epidemiologically significant cause of obesity (3 cases of leptin-gene mutation in humans accompanied by morbid obesity)
- Most of obese patients have hyperleptinemia i.e. circulating leptin levels correlate with body fat content
- Body weight loss induces decrease in circulating leptin levels
- Clinical trials focused on the treatment of obesity with leptin did not show significant benefit of leptin treatment to body weight loss

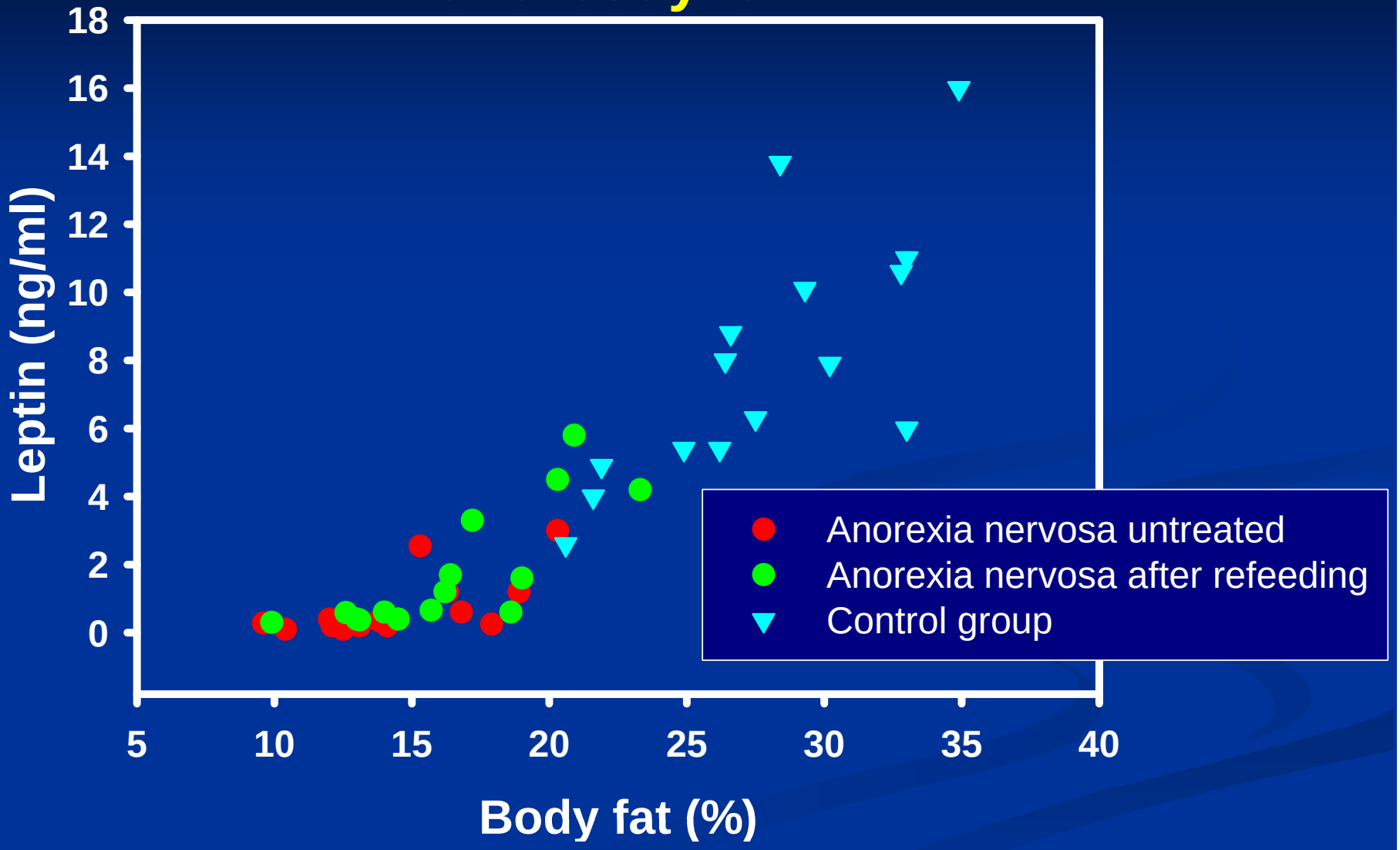
Leptin resistance phenomena vs. stronger role of leptin signalling in malnutrition rather than overnutrition

Why hyperleptinemia does not suppress food intake in patients with obesity?

- Resistance to leptin effects: either on the levels of leptin transport across the blood-brain barrier or on the postreceptor level

- Primary function of leptin is not to suppress food intake, but to trigger complex adaptive reaction of human body to starvation.

Correlation of serum leptin levels and body fat



Clinical application of leptin

- Under stabilized nutritional state very precise marker of body fat content
- Total leptin deficiency can be cause of morbid obesity in human
- Hypoleptinemia plays an important role as an initiator of complex neuroendocrine response on chronic malnutrition/fasting
- Substitution of leptin as a treatment of obesity or insulin resistance has not fulfilled expectations

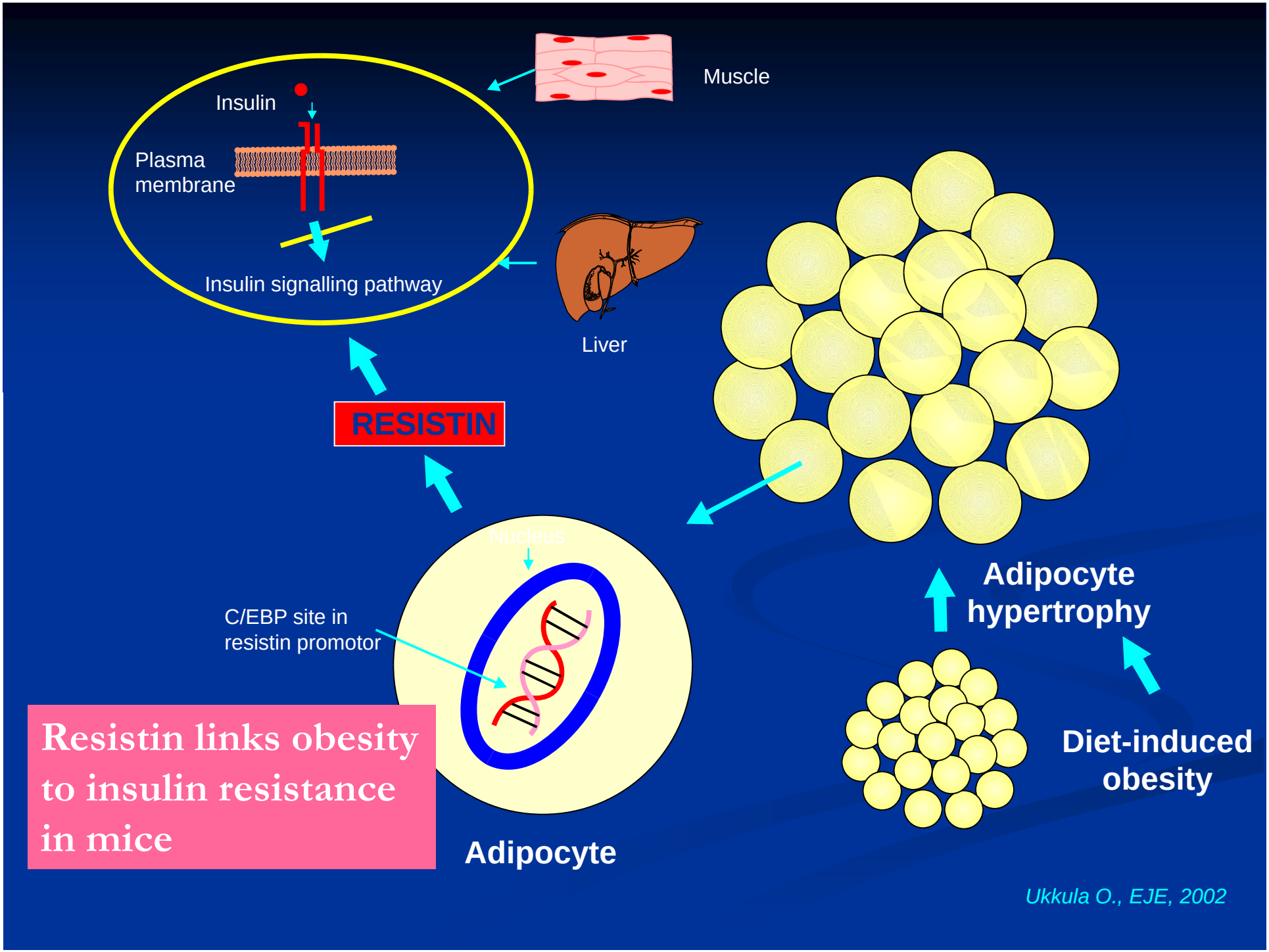
Resistin

Steppan et al, Nature, 2001:

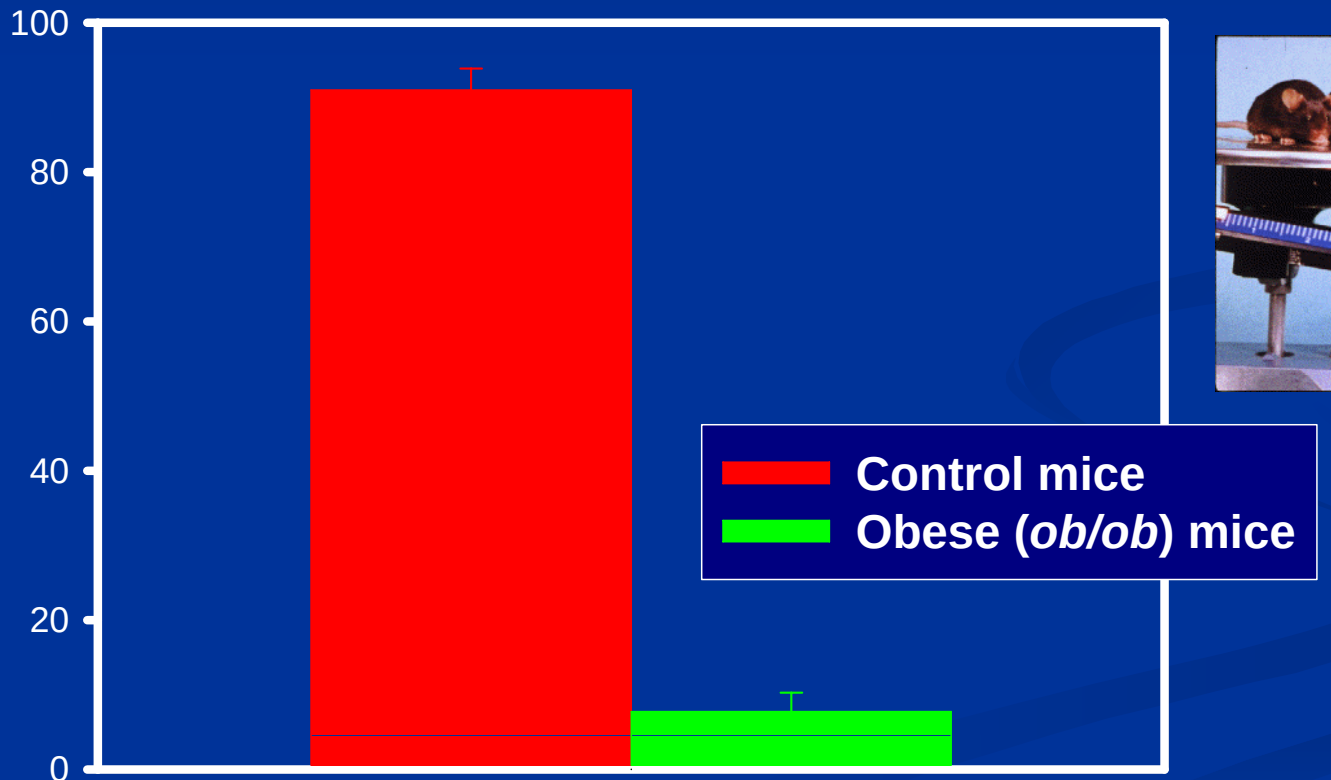
- Protein hormone produced by adipocytes
- Resistin administration in mice worsened glucose tolerance
- Anti-resistin antibody treatment increased insulin sensitivity

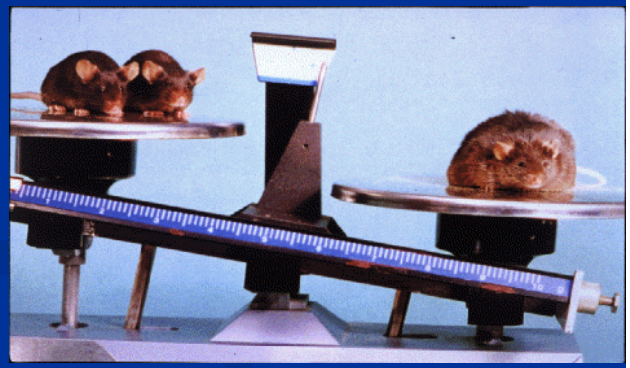
Rajala et al, JCI, 2003:

- In vivo resistin treatment selectively impaired liver insulin resistance in rats


Muscle
Insulin
Plasma membrane
Insulin signalling pathway
Liver
RESISTIN
Nucleus
C/EBP site in resistin promotor
Adipocyte
Adipocyte hypertrophy
Diet-induced obesity
Resistin links obesity to insulin resistance in mice
Ukkula O., EJE, 2002

BUT….Fat resistin mRNA is reduced in obese mice





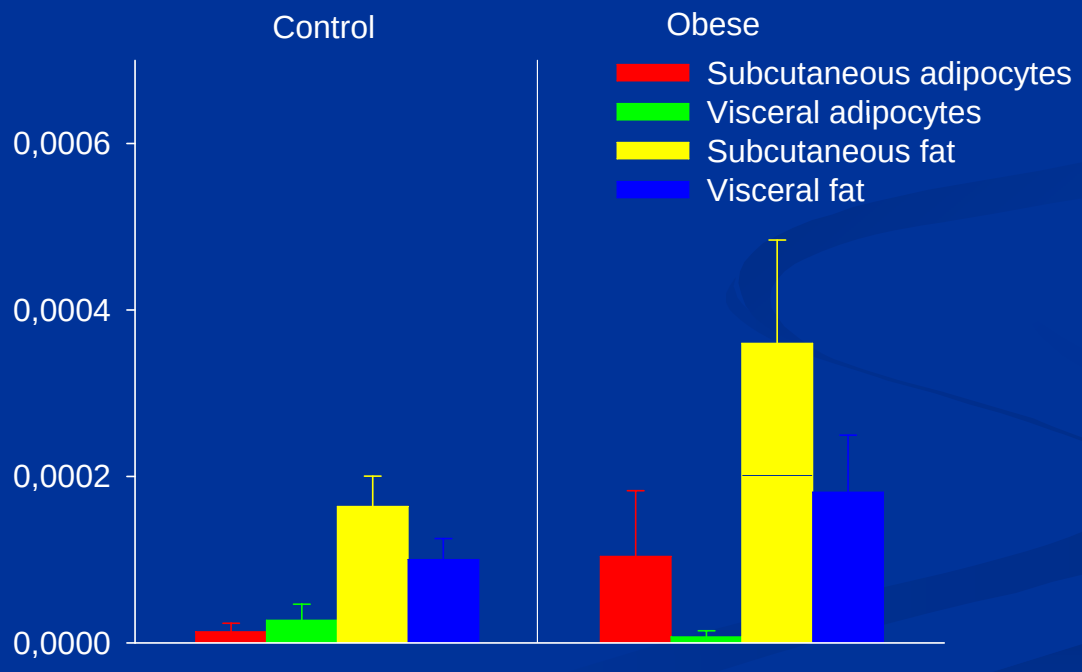
Haluzík et al, 2002

But in human obesity….

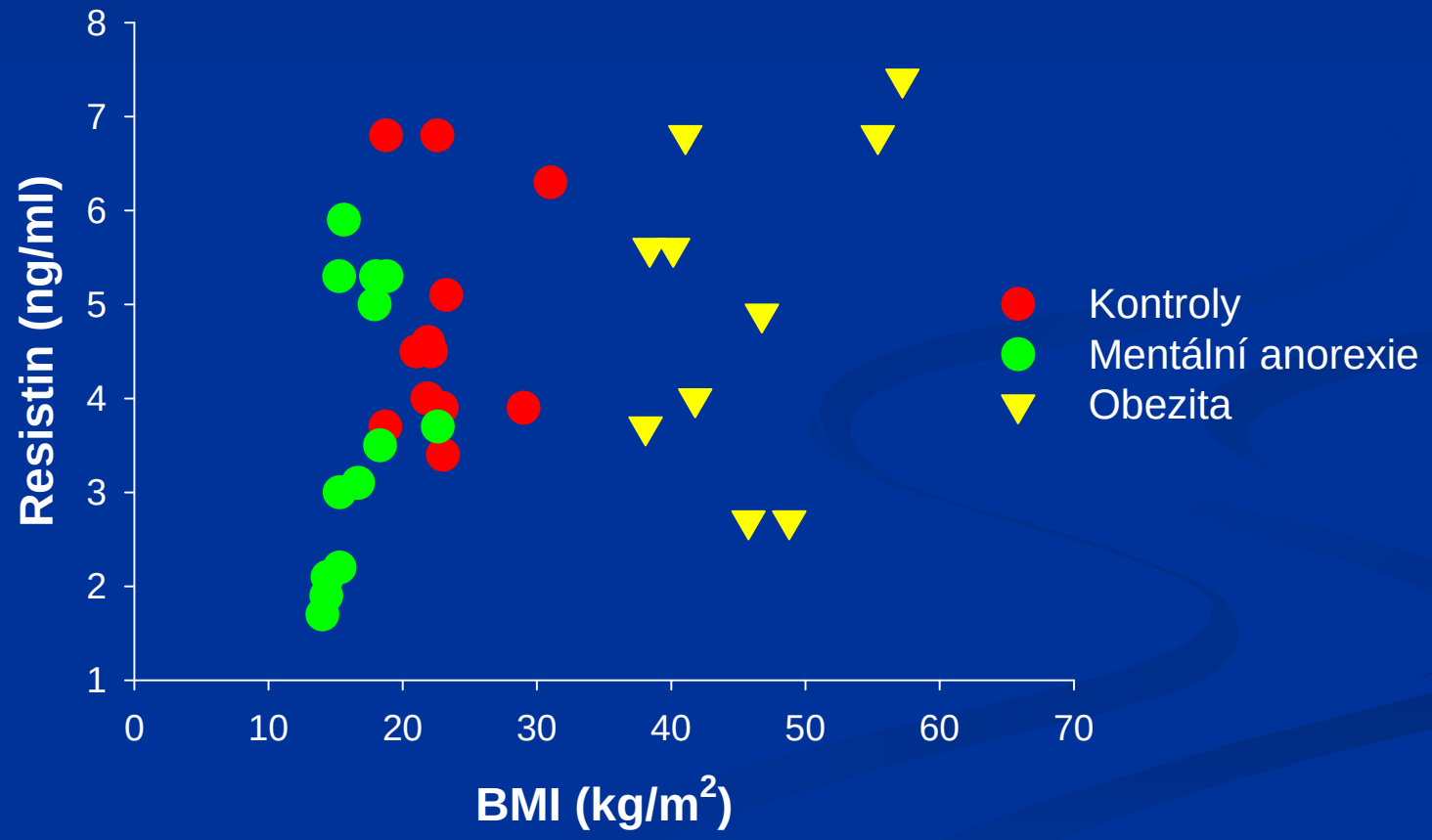
- Adipose resistin expression was even undetectable in some obese subjects (Nagaev, 2001)
- Resistin expression was increased only in whole adipose tissue samples but not in adipose cells lysates (Savage et al, 2001)
- Resistin in humans has probably proinflammatory than direct prodiabetic effects and is produced predominantly by macrophages

Resistin is produced predominantly by stroma-vascular (non-adipocyte) fraction of adipose tissue – namely macrophages and other immunocompetent cells

Resistin mRNA expression

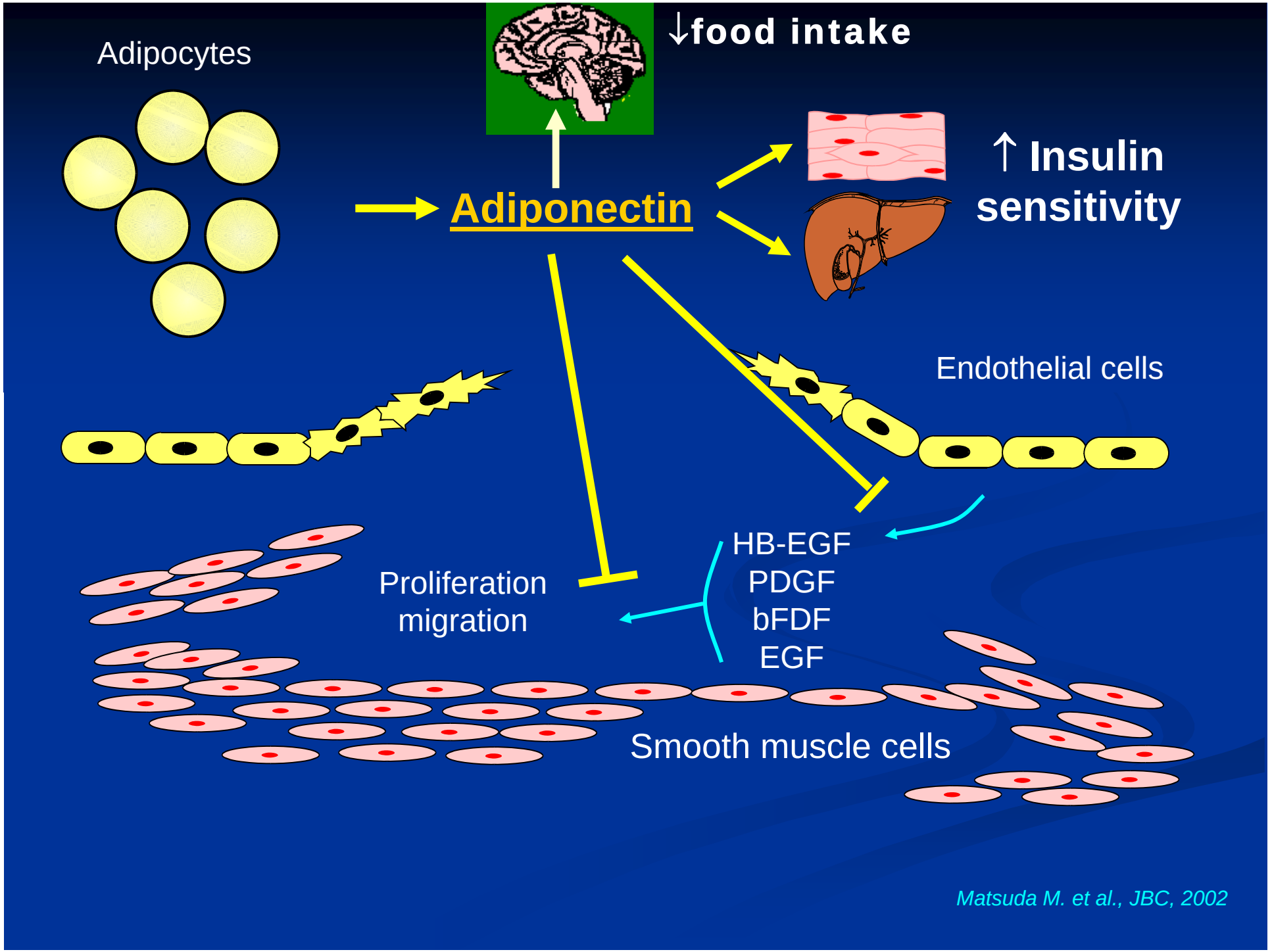


Correlation of plasma resistin levels and body mass index

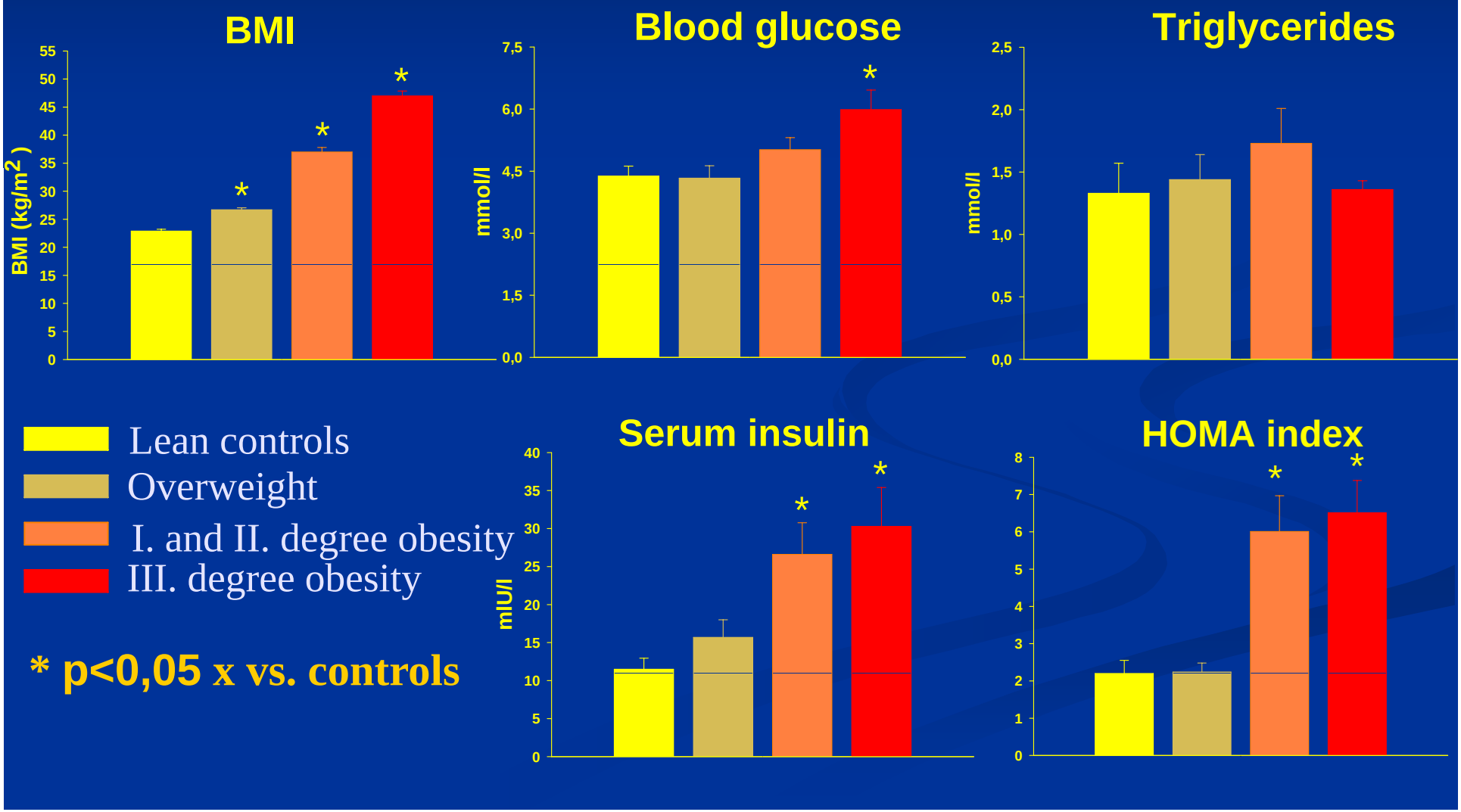


Adiponectin – one of the few fat hormones with positive metabolic effects

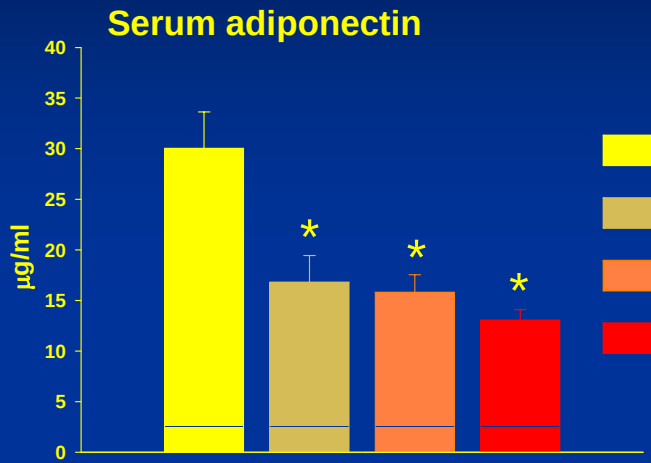
- Adipose tissue-derived protein
- Circulating adiponectin levels are decreased in patients with obesity, type 2 diabetes mellitus, and patients with coronary heart disease
- Adiponectin treatment increased insulin sensitivity in both obese and lipoatrophic mice
- Adiponectin exerts antiatherogenic and antiinflammatory effects
- Adiponectin knockout mice have mild insulin resistance and accelerated atherosclerosis


Adipocytes
↓food intake
Adiponectin
↑ Insulin sensitivity
Endothelial cells
HB-EGF
PDGF
bFDF
EGF
Proliferation
migration
Smooth muscle cells
Matsuda M. et al., JBC, 2002

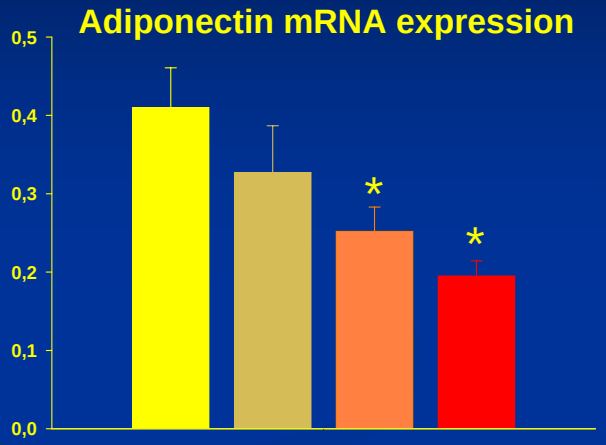
Patients characteristics



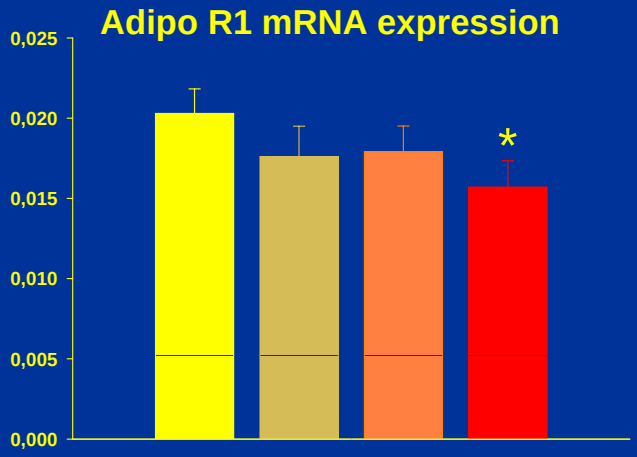
Serum adiponectin concentrations and mRNA expression of adiponectin and its receptors in subcutaneous adipose tissue

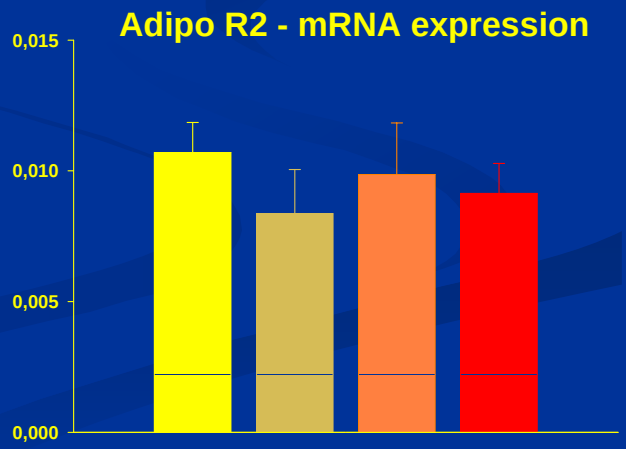


Control
Overweight
I. and II. degree obesity
III. degree obesity



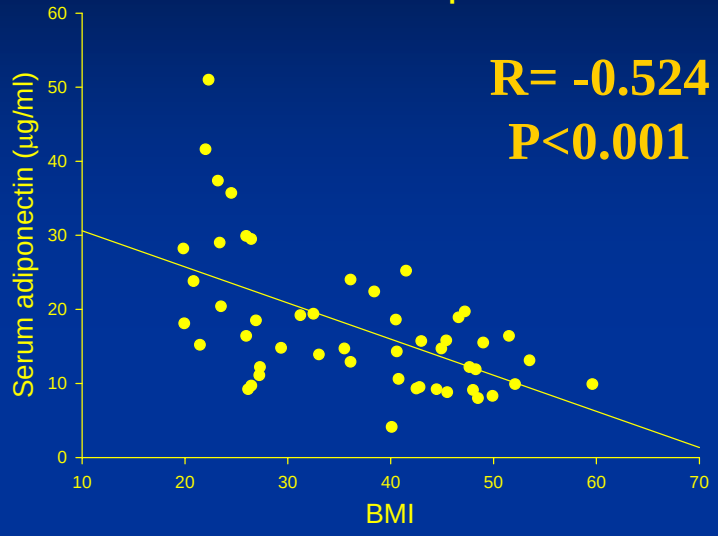
*** p<0.05 x vs. control**





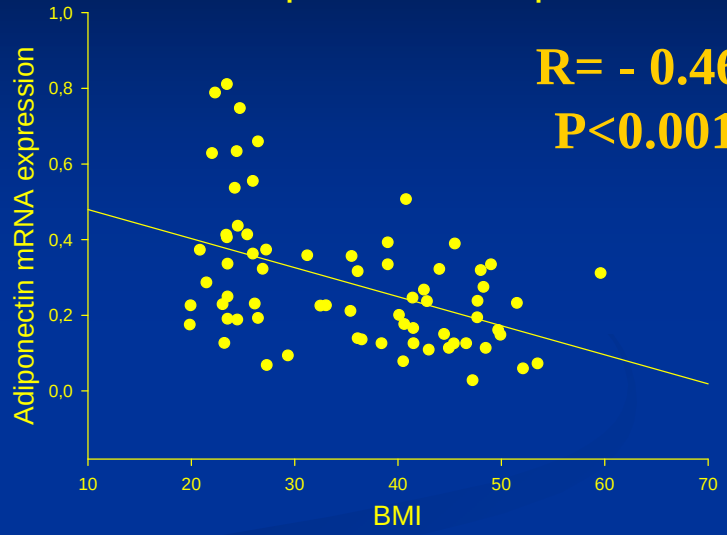
Correlation of serum adiponectin, subcutaneous adiponectin mRNA and adiponectin receptors mRNA expression with BMI

Correlation of serum adiponectin and BMI



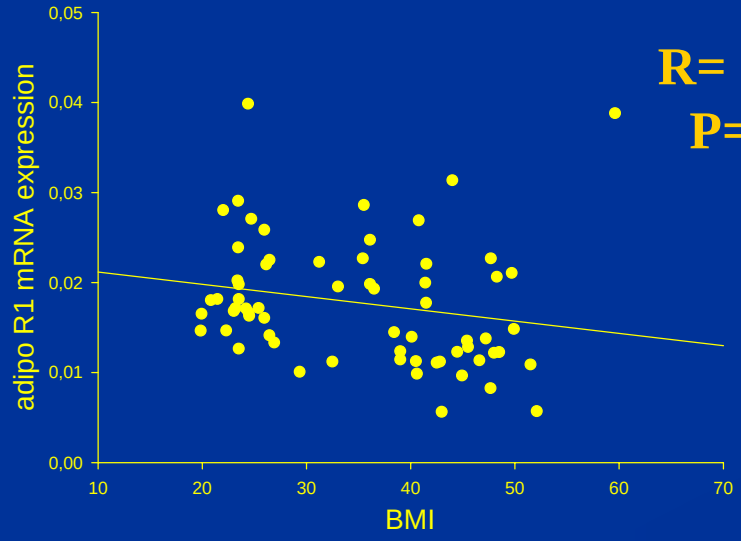
R= -0.524
P<0.001

Correlation of adiponectin mRNA expression and BMI



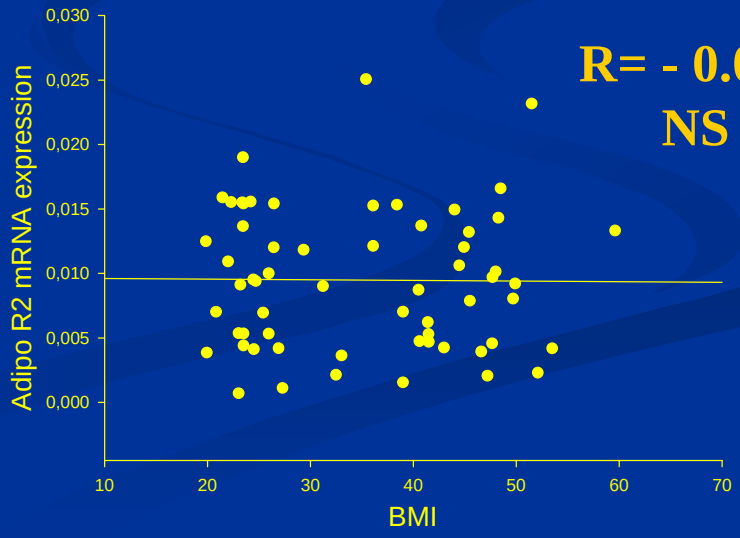
R= - 0.46
P<0.001

Correlation of adipo R1 mRNA expression and BMI



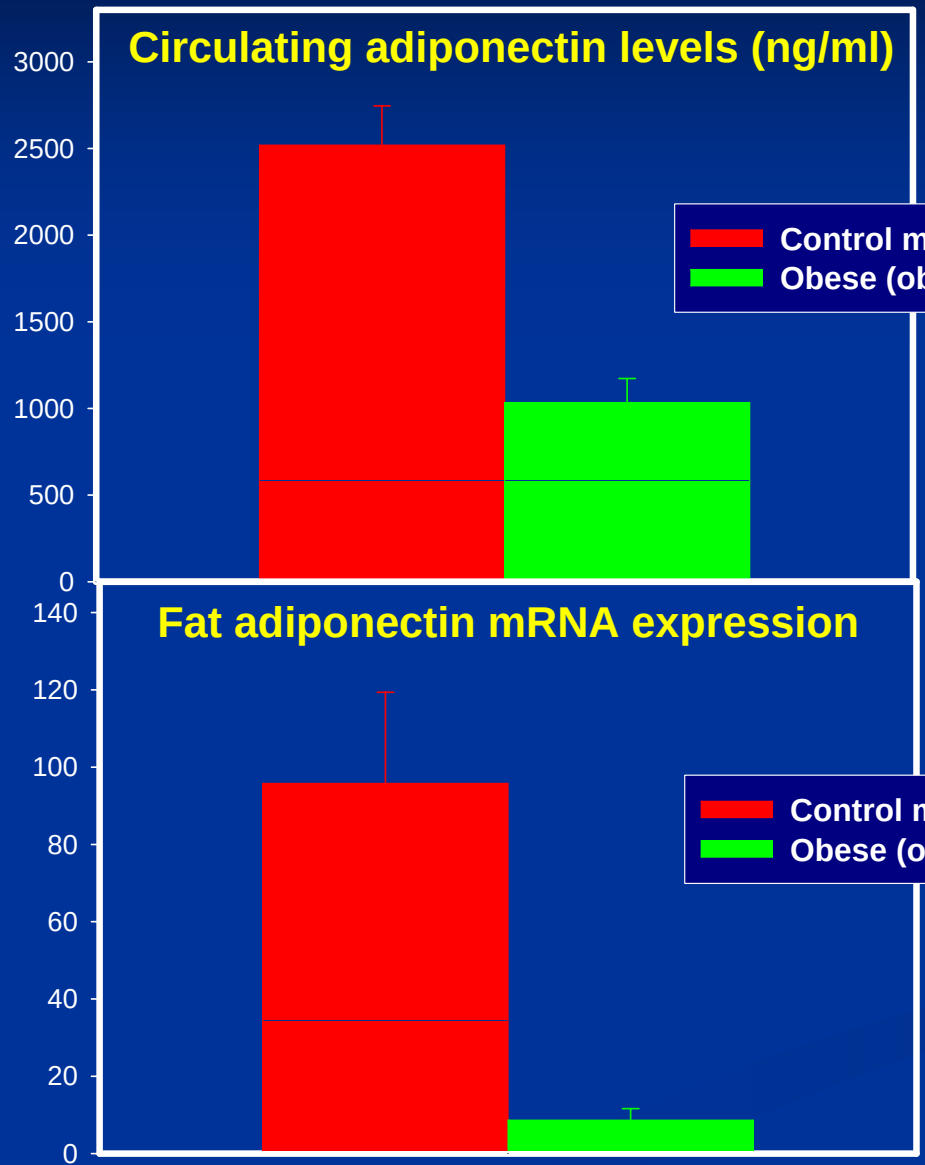
R= - 0.354
P=0.004

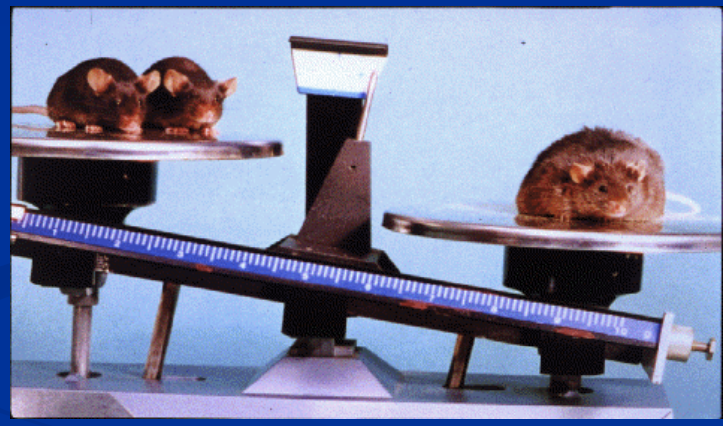
Correlation of adipo R2 mRNA expression and BMI



R= - 0.076
NS

Obesity in mice is accompanied by decreased adiponectin





Haluzik et al, 2003

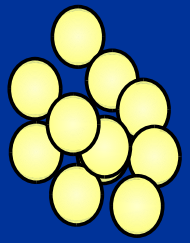
Clinical importance of adiponectin

- Adiponectin strongly correlates with insulin sensitivity and with endothelial (dys)function
- ? Application as an early marker of endothelial dysfunction
- Deficit of adiponectin can have etiopathogenetic relationship with the insulin resistance syndrome
- Substitution of adiponectin could be one of ways to prevent and/or treat insulin resistance syndrome

Ectopic fat storage syndrome

“Good” genes and healthy life style

+



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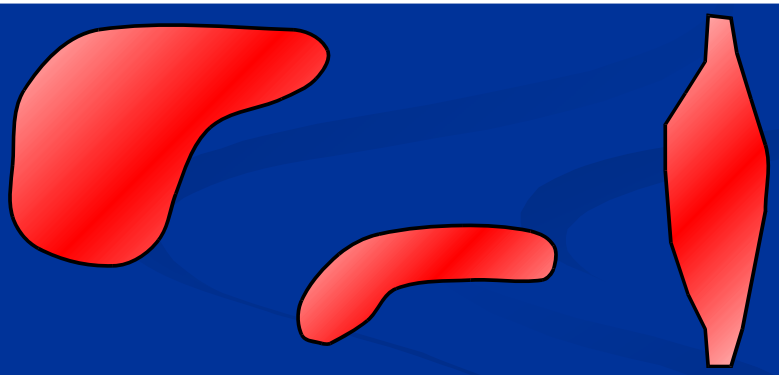


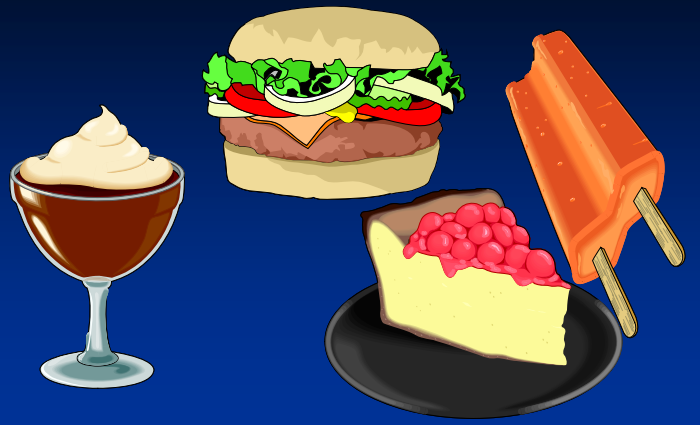
Small
adipocytes

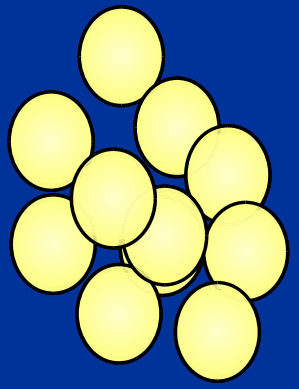
Minimal ectopic fat
in liver, beta cell
and skeletal muscle

Ravussin et al., 2002

“Bad” genes and/or unhealthy life style

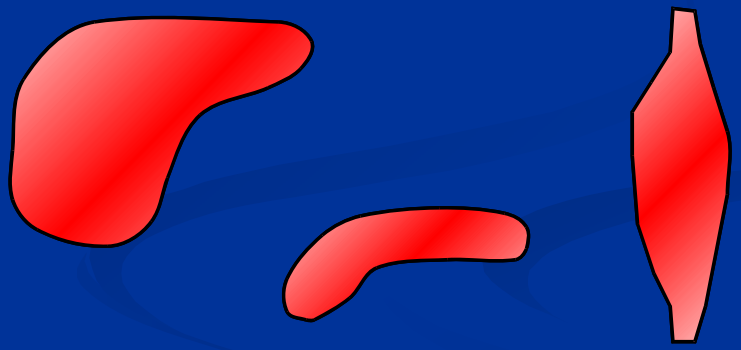
+





Enlarged adipocytes
Endocrine dysfunction

+



Increased ectopic fat
in liver, beta cell
and skeletal muscle

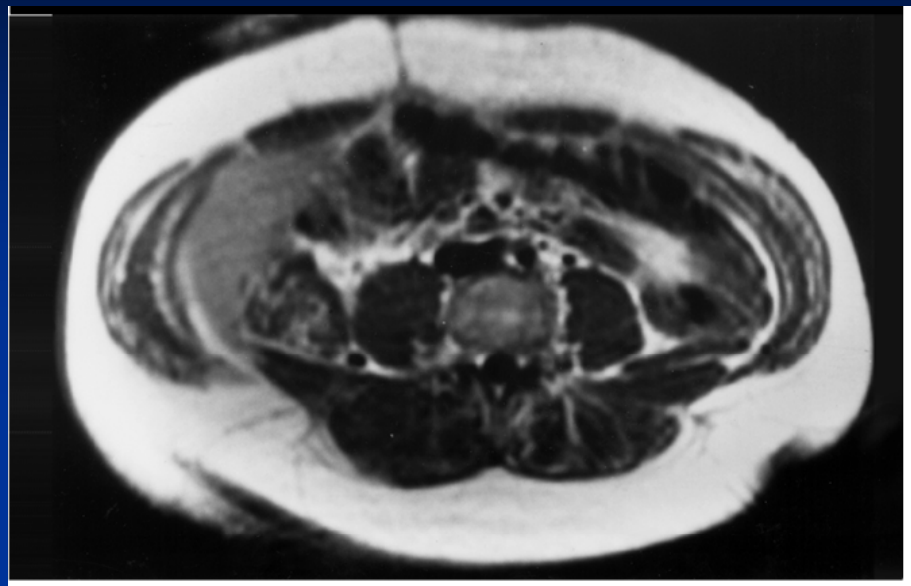
Insulin resistance, type 2 diabetes

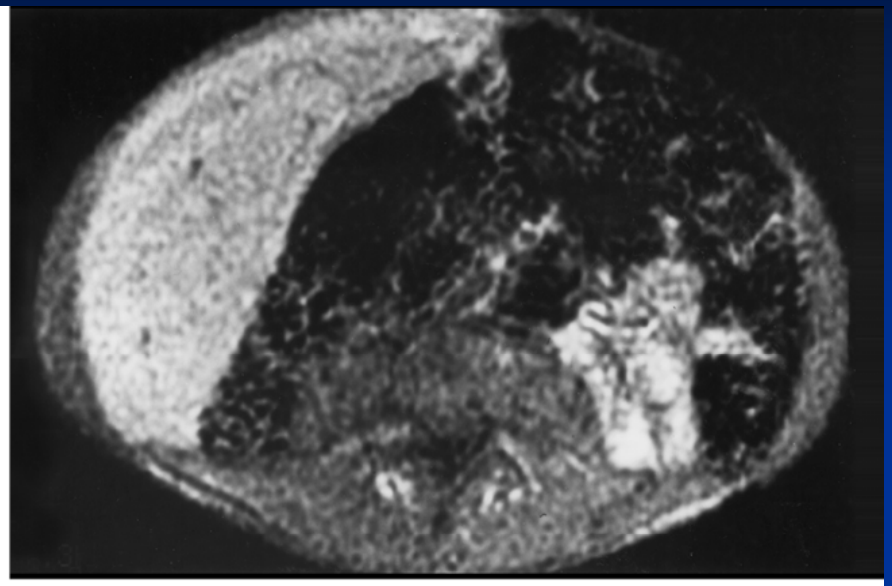
Human lipoatrophy/lipodystrophy

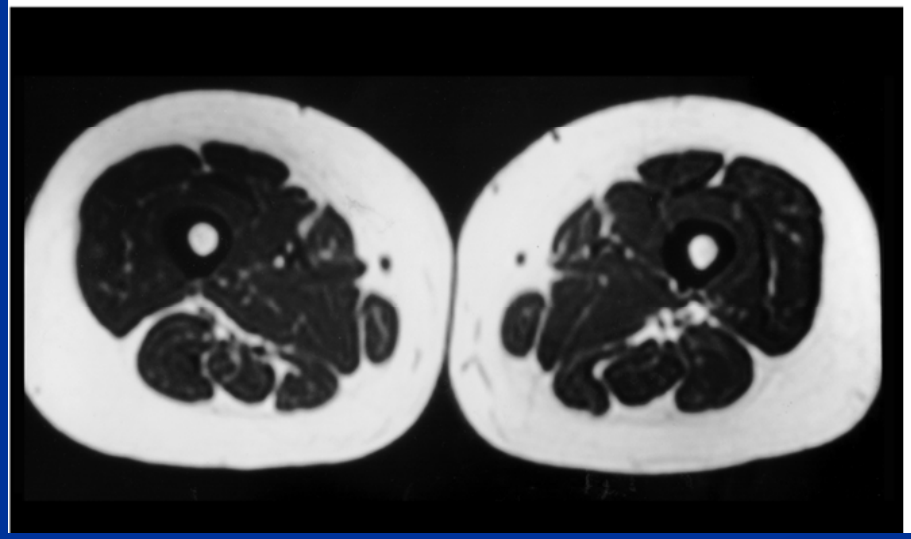
- Heterogeneous group of diseases
- Fat loss: generalized, partial, and localized
- Redistribution of fat in some cases
- Etiology: genetic, autoimmune, other
- Onset: congenital, puberty, other
- Metabolic severity roughly correlates with degree of fat loss

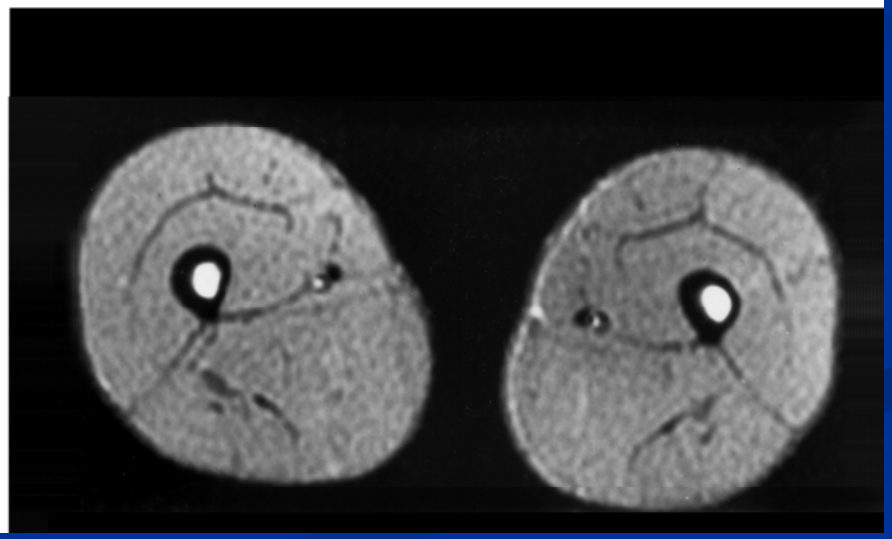
Normal

Lipoatrophic



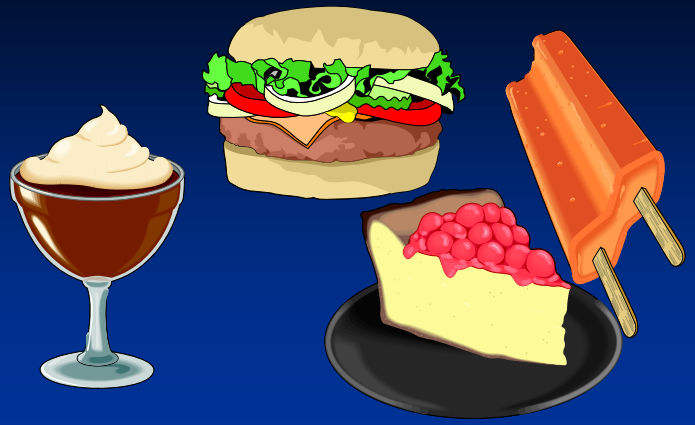


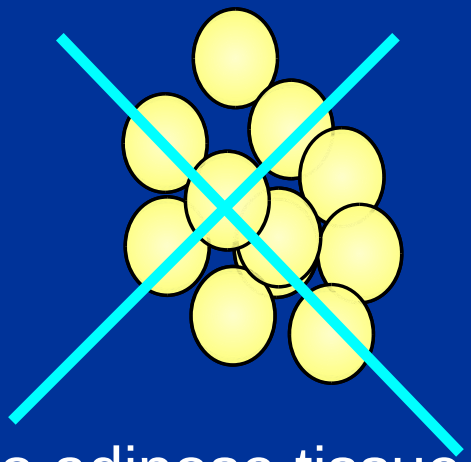




Genetic factors or other causes (retroviral therapy in HIV)

+





No adipose tissue
No adipose tissue-derived hormones

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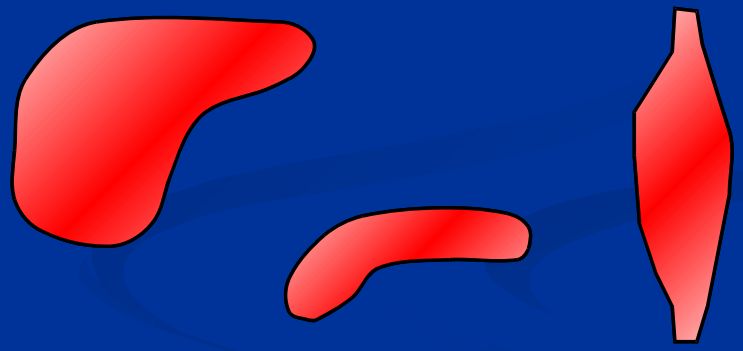


Increased ectopic fat
in liver, beta cell
and skeletal muscle

Insulin resistance, type 2 diabetes

Both too fat and too lean mouse have similar pattern of metabolic abnormalities and both have health complications

***ob/ob* mice**
(mutation of leptin gene)

A-ZIP/F-1 mice (total absence of white adipose tissue)

Fenotypic features od morbid obesity (*ob/ob* mice) and lipoatrophy (A-ZIP/F-1 mouse)

ob/ob mouse

- Total absence of leptin
- Hyperfagia, morbid obesity
- Increased levels of TGL, FFA
- Ectopic lipid storage (muscle, liver, pancreas)
- Extreme insulin resistance/diabetes
- Reduced BMR, infertility
- Increased corticosterone

A-ZIP/F-1 mouse

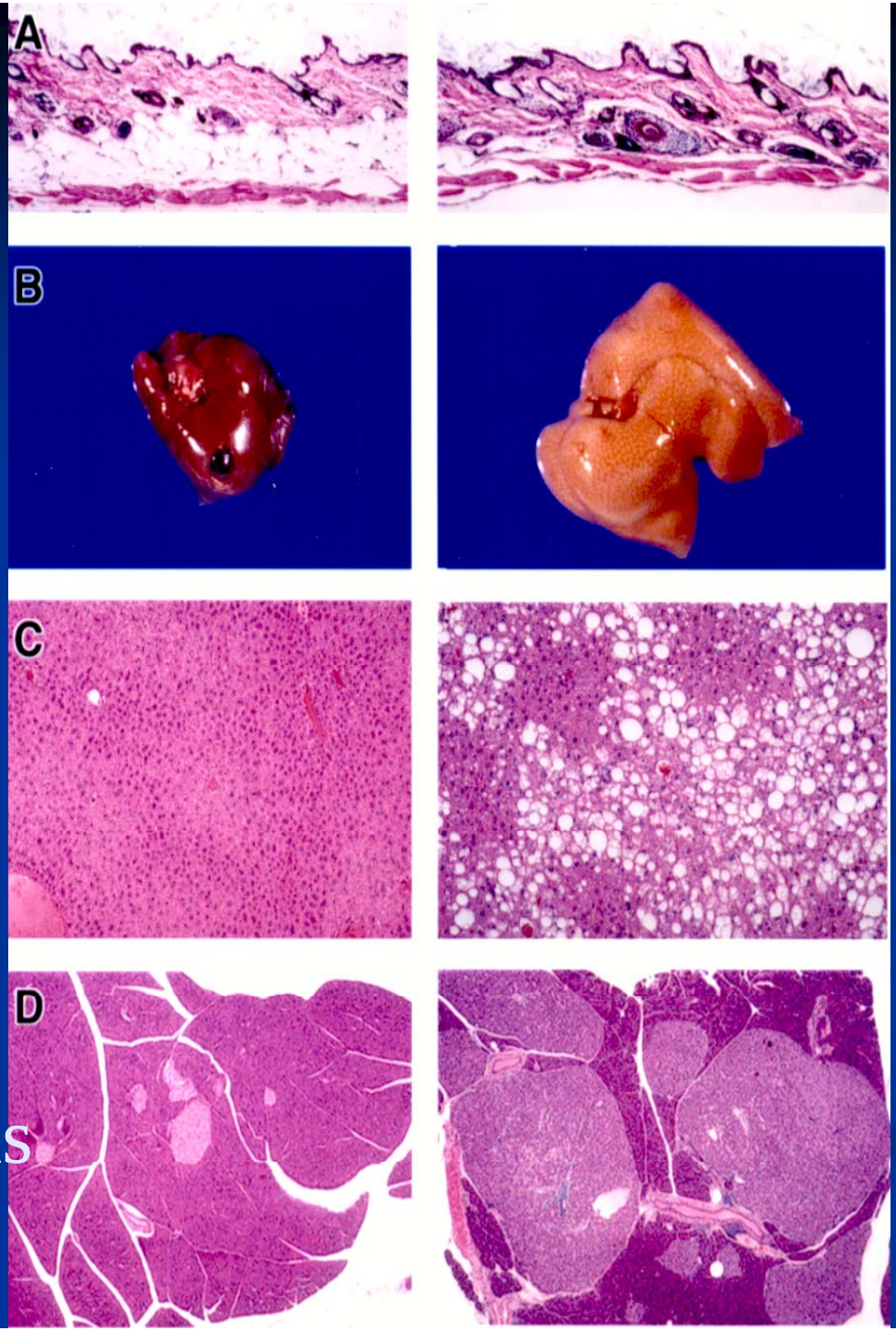
- Total absence of white adipose tissue, total absence of all adipose tissue hormones
- Hyperfagia
- Increased levels of TGL, FFA
- Ectopic lipid storage (muscle, liver, pancreas)
- Extreme insulin resistance/diabetes
- Reduced BMR, infertility
- Increased corticosterone

Skin

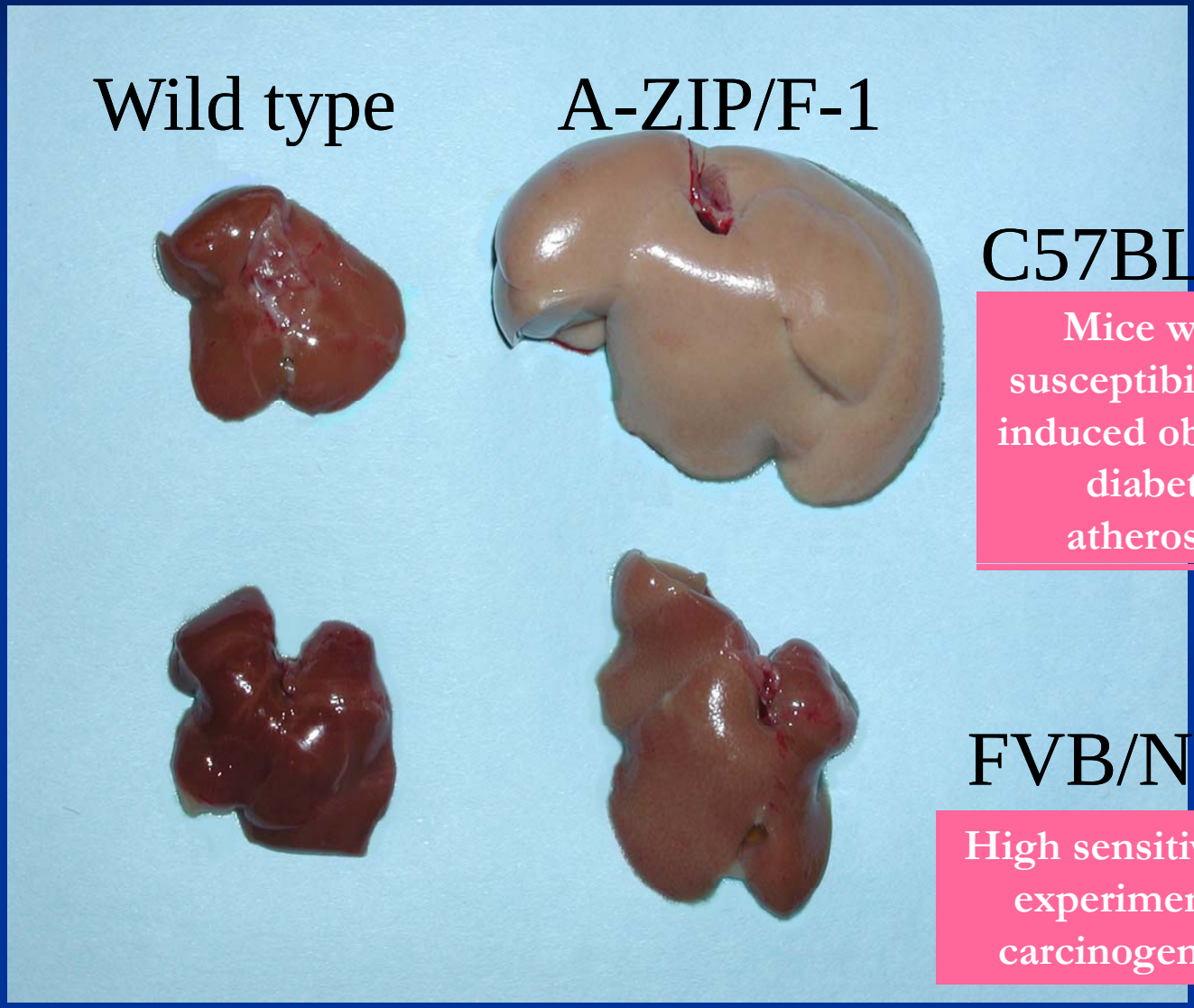
Liver

Liver

Pancreas



Effect of genetic background (modification genes) on liver steatosis in A-ZIP/F-1 mice



C57BL/6J

Mice with high susceptibility to diet-induced obesity, type2 diabetes and atherosclerosis

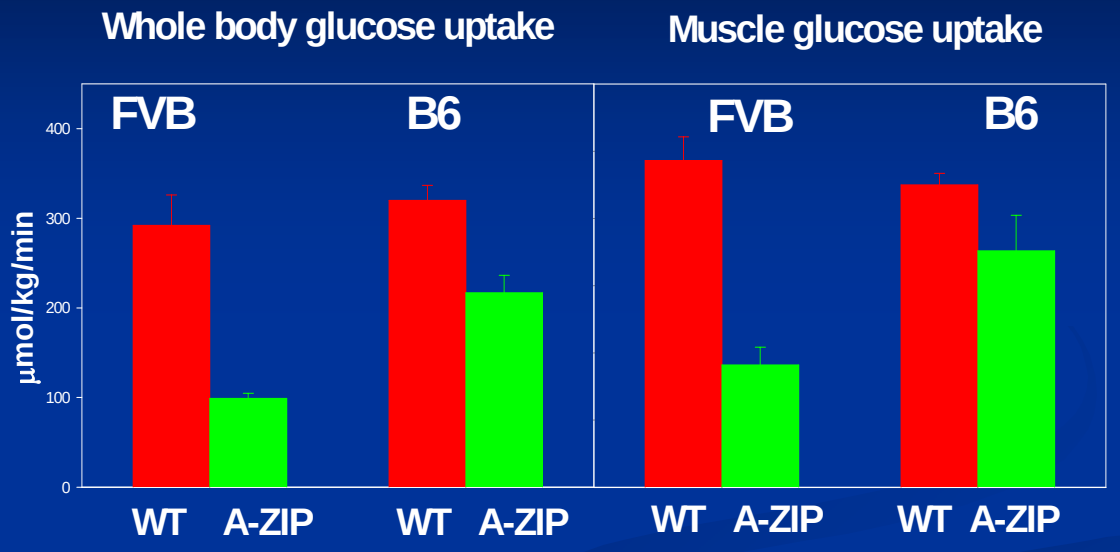
FVB/N

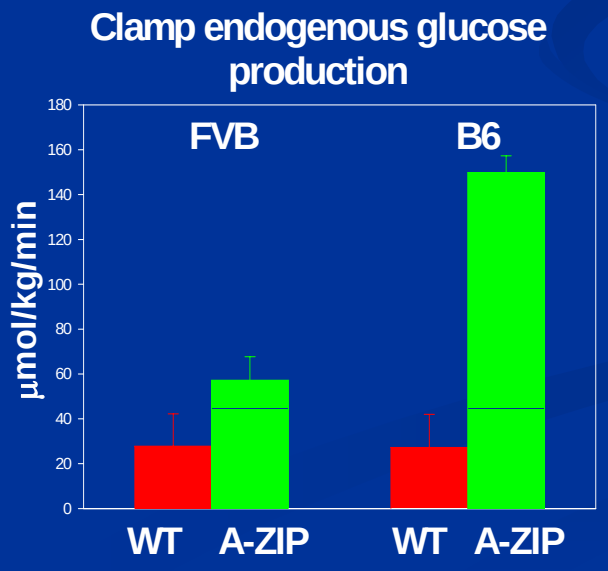
High sensitivity to experimental carcinogenesis

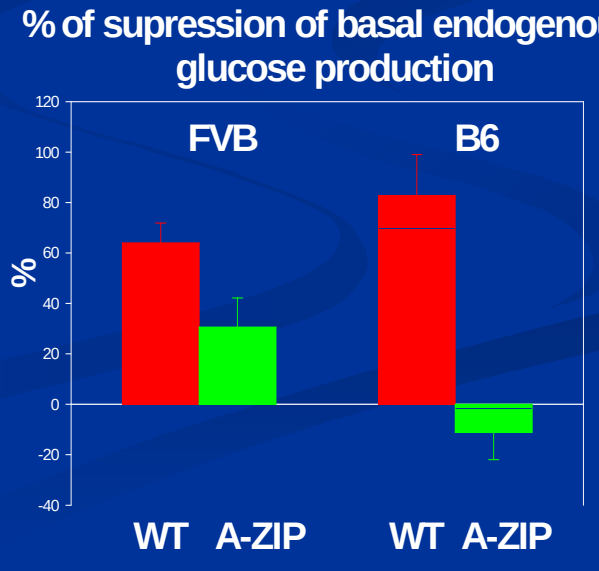
Effect of modification genes on insulin sensitivity in lipoatrophic A-ZIP/F-1 mice

FVB - High sensitivity to experimental carcinogenesis

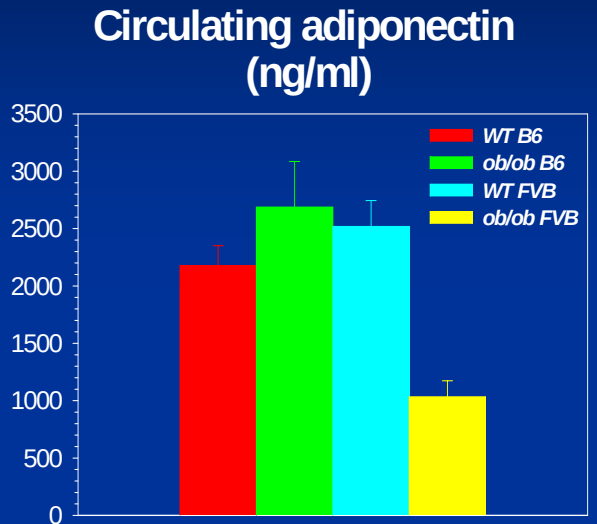
B6 - Mice with high susceptibility to diet-induced obesity, type2 diabetes and atherosclerosis

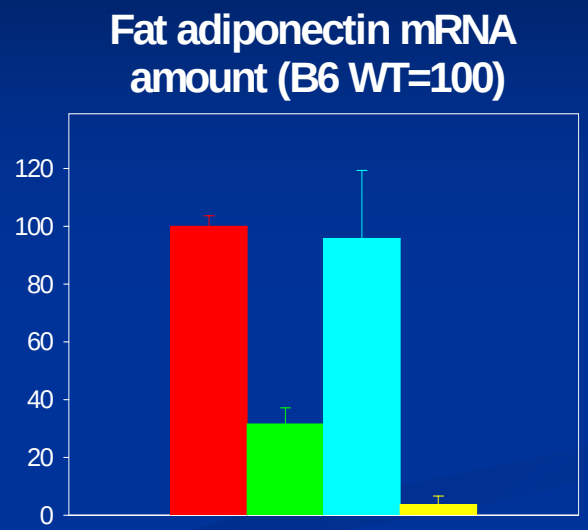


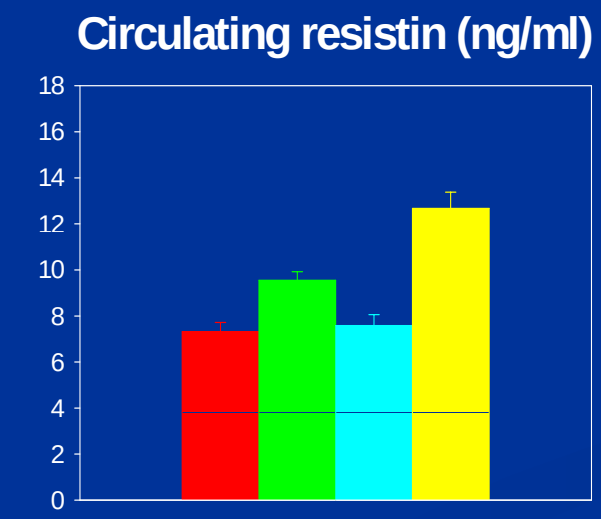


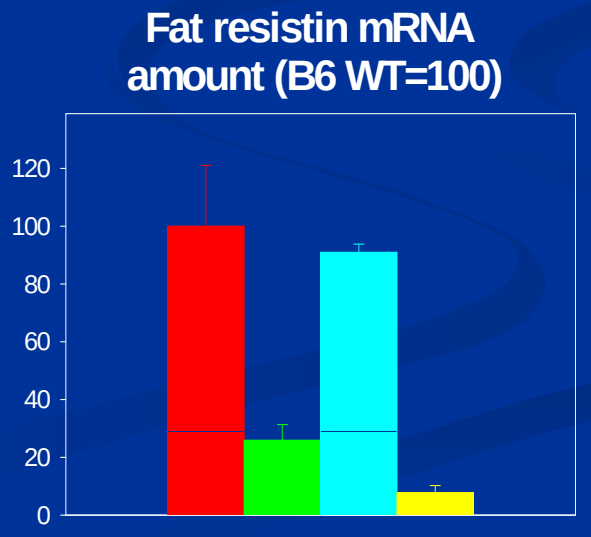


mRNA expression and concentrations of adipocyte hormones in *ob/ob* mice

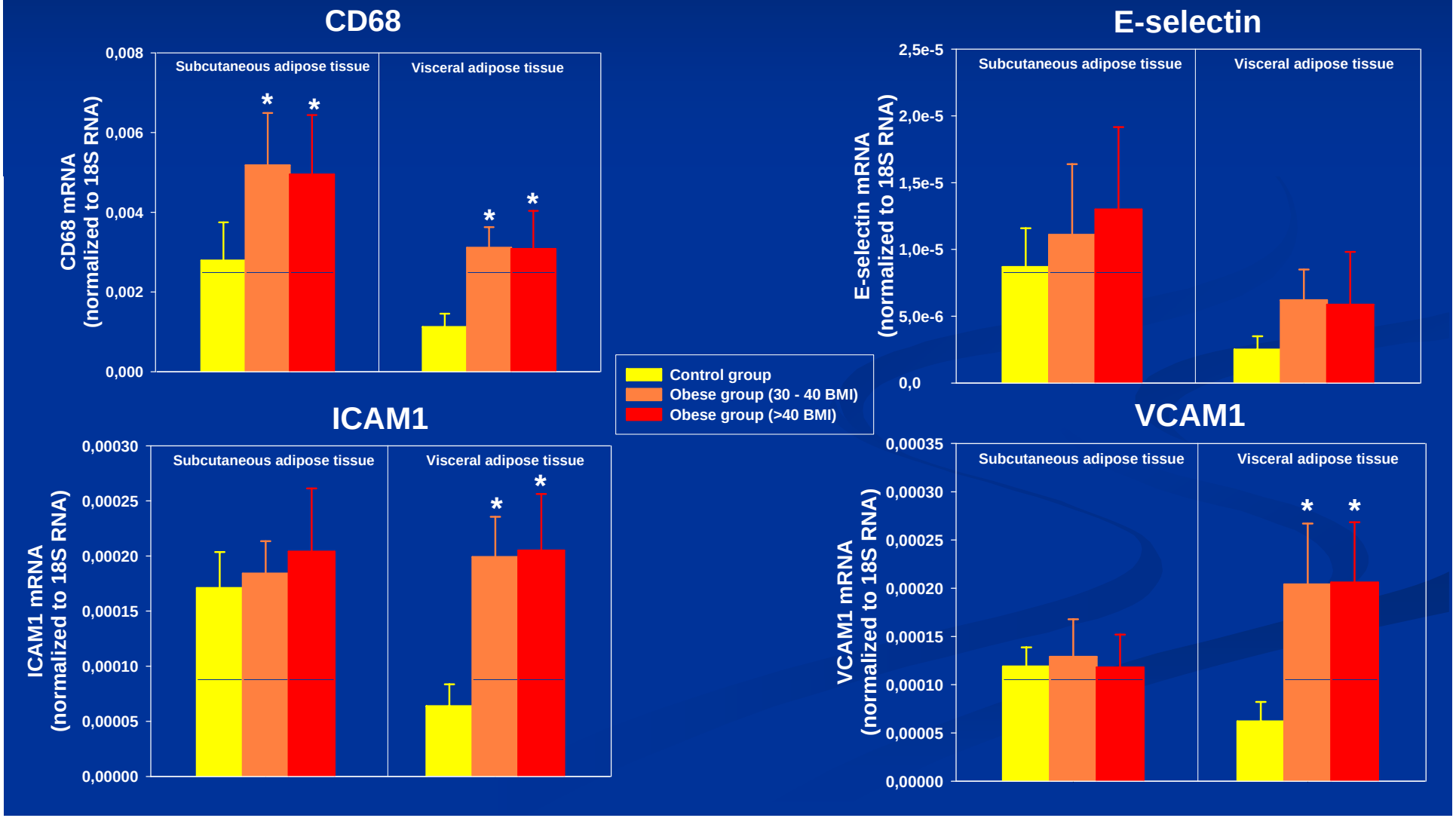








FAT adhesion molecules expression is increased in obesity



How important is the disrubted endocrine function of adipose tissue in the etiopatogenesis of insulin resistance/metabolic syndrome?

Leptin

- Total deficit has absolutely crucial metabolic implications, but is extremely uncommon
- Partial deficit can be of importance in a part of obese patients, but the clear evidence of the beneficial effect of leptin substitution is lacking
- To date knowledge about leptin does not confirm the importance of its measurement or substitution in clinical setting

Resistin

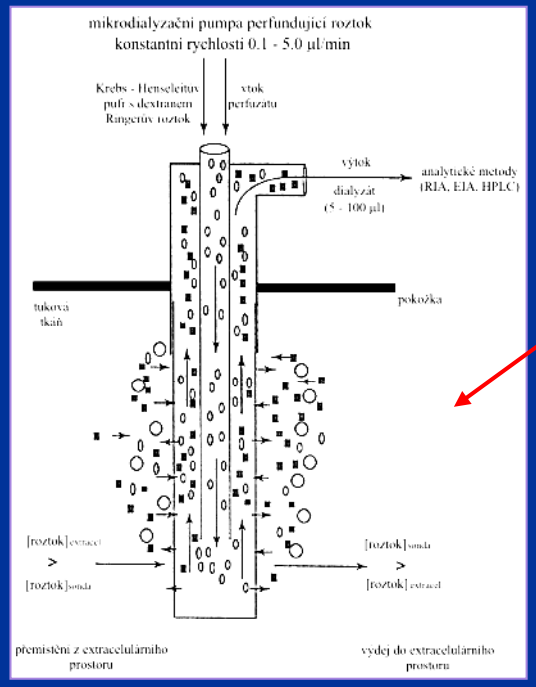
- The original hypothesis about etiopathogenetic role of resistin in the development of insulin resistance associated with obesity is not unitary confirmed
- Clinical application is not clear yet

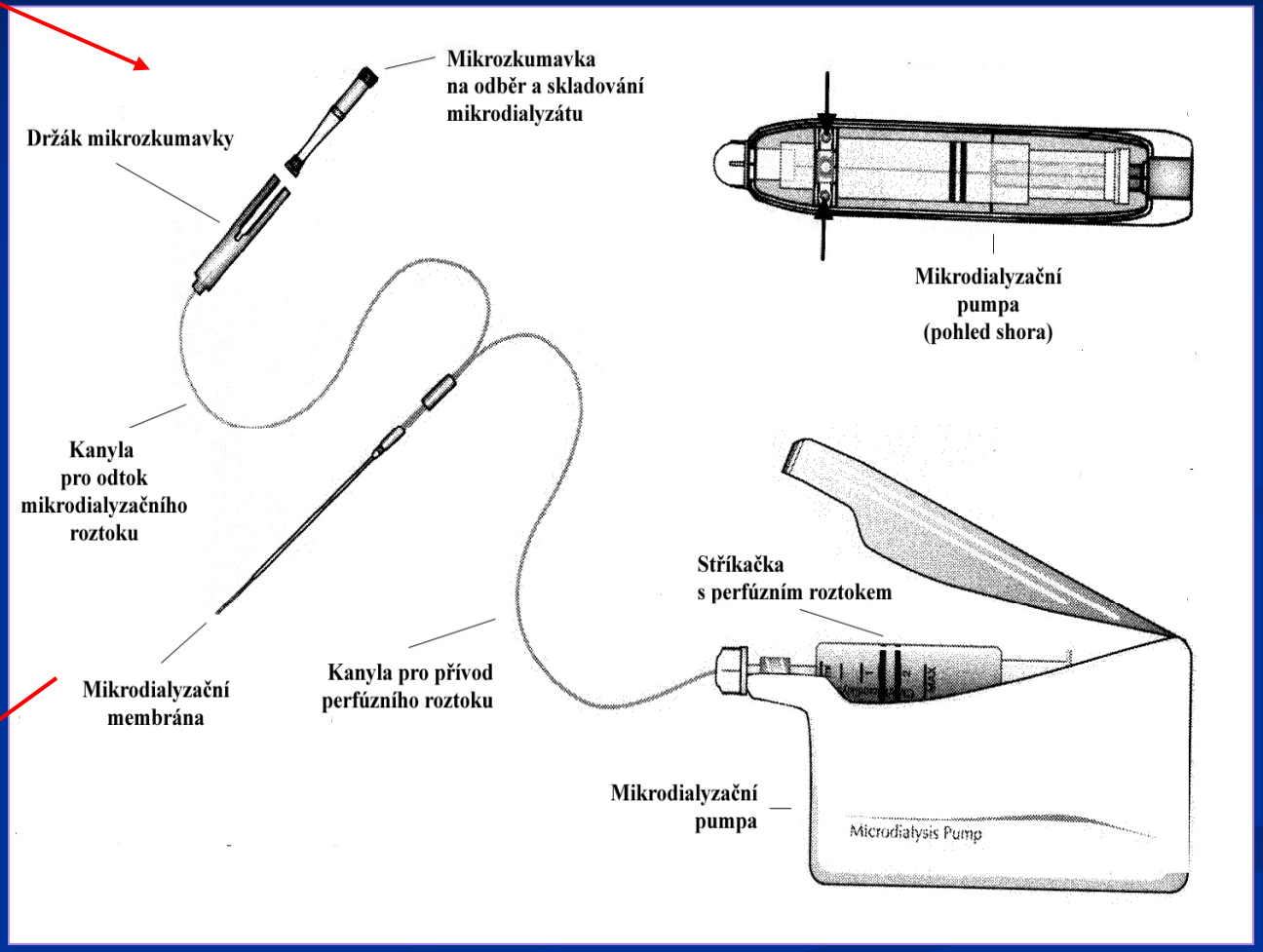
Adiponectin

- Most perspective adipocytokine in a way of therapeutic use
- Measurement of serum adiponectin concentrations as a criterion of insulin sensitivity and/or endothelial dysfunction? – further studies needed
- Administration of adiponectin could theoretically influnce minimally two components of IRS – insulin resistance a dyslipidemia
- Administration of adiponectin could also potentially decrease the risk of cardiovascular complications in MS

In vivo microdialysis is a new technique for continuous monitoring of tissue metabolism

Principle of microdialysis





Conclusions

- Adipose tissue produces numerous bioactive compounds that directly or indirectly affect energy homeostasis and metabolic regulations
- Immunocompetent cells residing in adipose tissue contribute to overall activation of immune system by different stimuli
- Excess of adipose tissue in obesity shifts its endocrine profile towards increased production of metabolically harmful factors
- Disturbed endocrine function of adipose in concert with other factors markedly contributes to increased risk of morbidity and mortality in patients with obesity