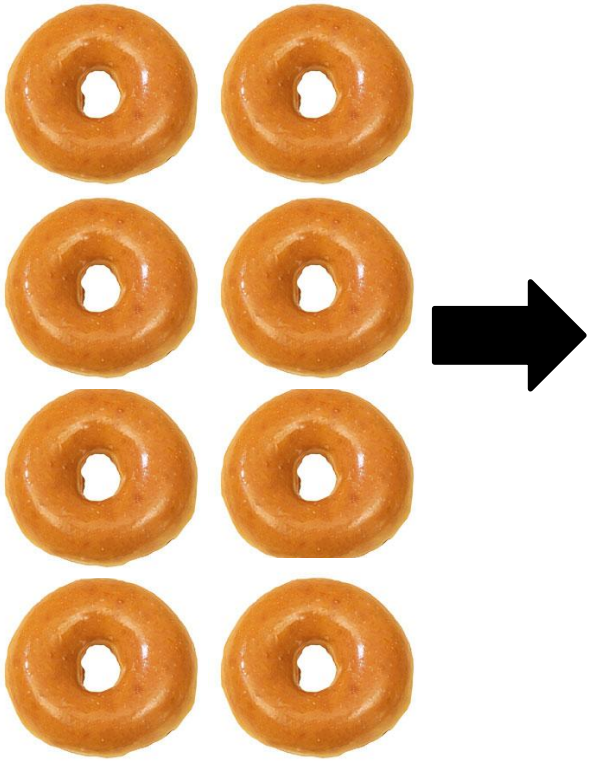
Physiology of Adipose Tissue: Fat, Adipokines, Obesity…Oh My



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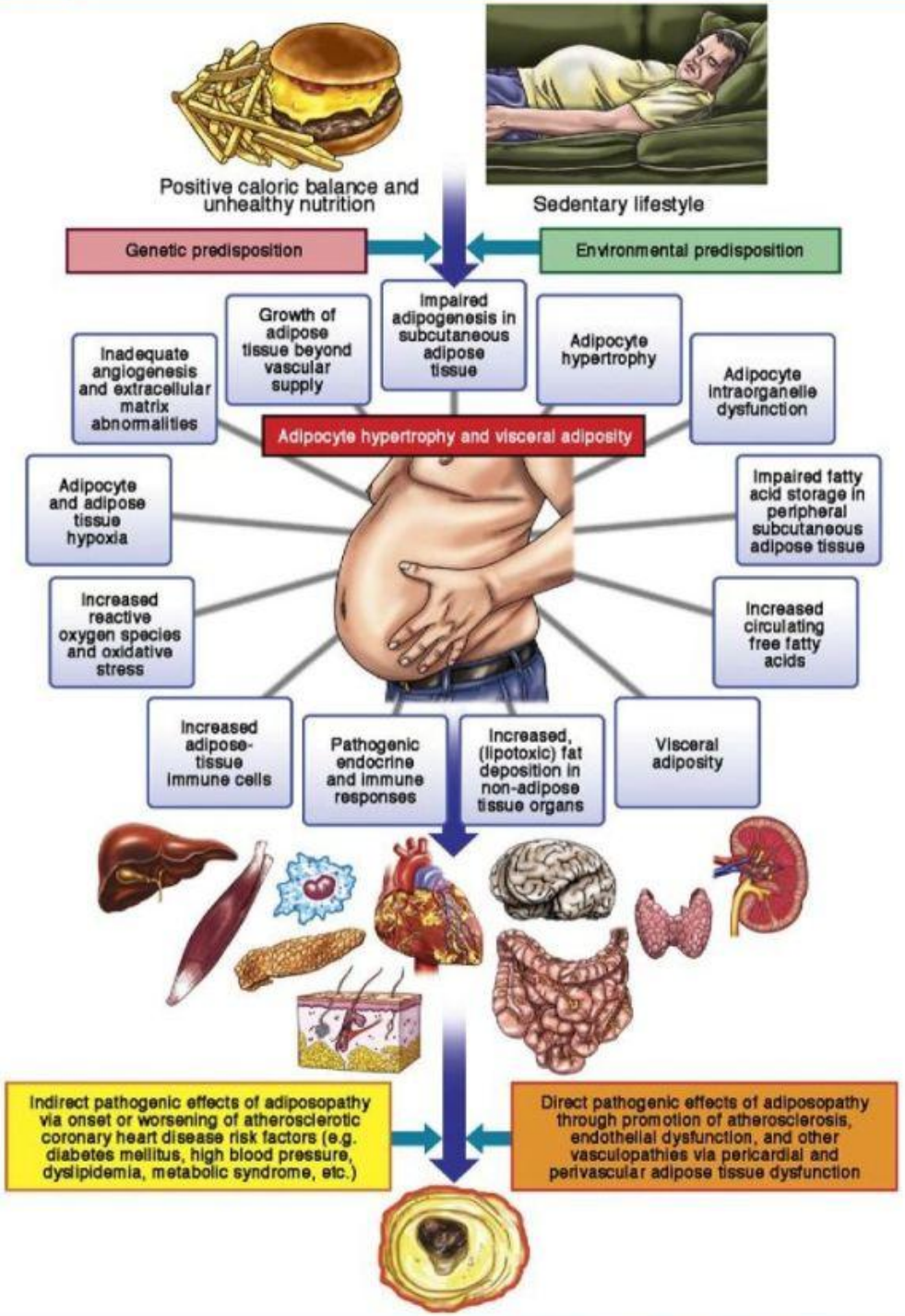
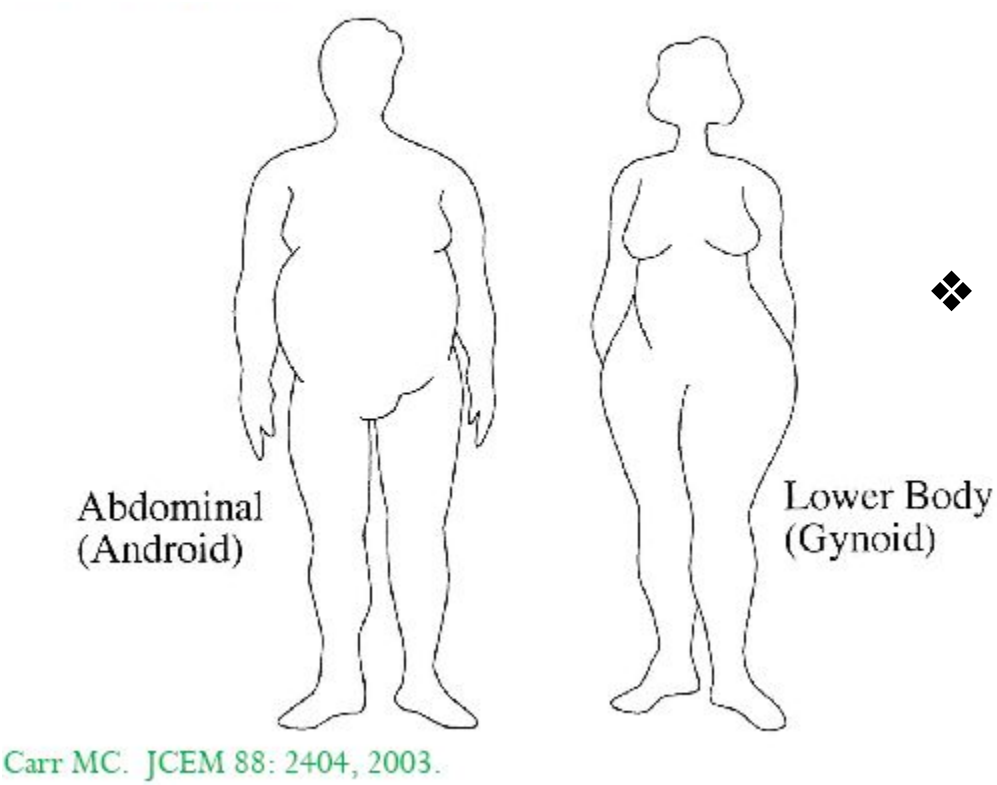

Positive caloric balance and unhealthy nutrition
Sedentary lifestyle
Genetic predisposition
Environmental predisposition
Impaired adipogenesis in subcutaneous adipose tissue
Growth of adipose tissue beyond vascular supply
Adipocyte hypertrophy
Inadequate angiogenesis and extracellular matrix abnormalities
Adipocyte intraorganelle dysfunction
Adipocyte hypertrophy and visceral adiposity
Adipocyte and adipose tissue hypoxia
Impaired fatty acid storage in peripheral subcutaneous adipose tissue
Increased reactive oxygen species and oxidative stress
Increased circulating free fatty acids
Increased adipose-tissue immune cells
Pathogenic endocrine and immune responses
Increased, (lipotoxic) fat deposition in non-adipose tissue organs
Visceral adiposity
Indirect pathogenic effects of adiposopathy via onset or worsening of atherosclerotic coronary heart disease risk factors (e.g. diabetes mellitus, high blood pressure, dyslipidemia, metabolic syndrome, etc.)
Direct pathogenic effects of adiposopathy through promotion of atherosclerosis, endothelial dysfunction, and other vasculopathies via pericardial and perivascular adipose tissue dysfunction

Adipose History

- Thought to lack any specific metabolic activity, thus received little attention until ~1990s
- Thought to be a inert storage depot regulated by adrenergic stimulation. This view remained prevalent until research focused attention on the relevant role of adipose tissue as a source of metabolic fuel.
- Recently, adipose tissue biology has emerged in relation to the discovery of a host of adipocyte derived factors that contribute to energy homeostasis.
- Now well established that several factors and cytokines secreted by adipose tissue play a key role in cell differentiation, energy metabolism and insulin resistance!

Shift in Body Fat Distribution in Diabetes

- Apple

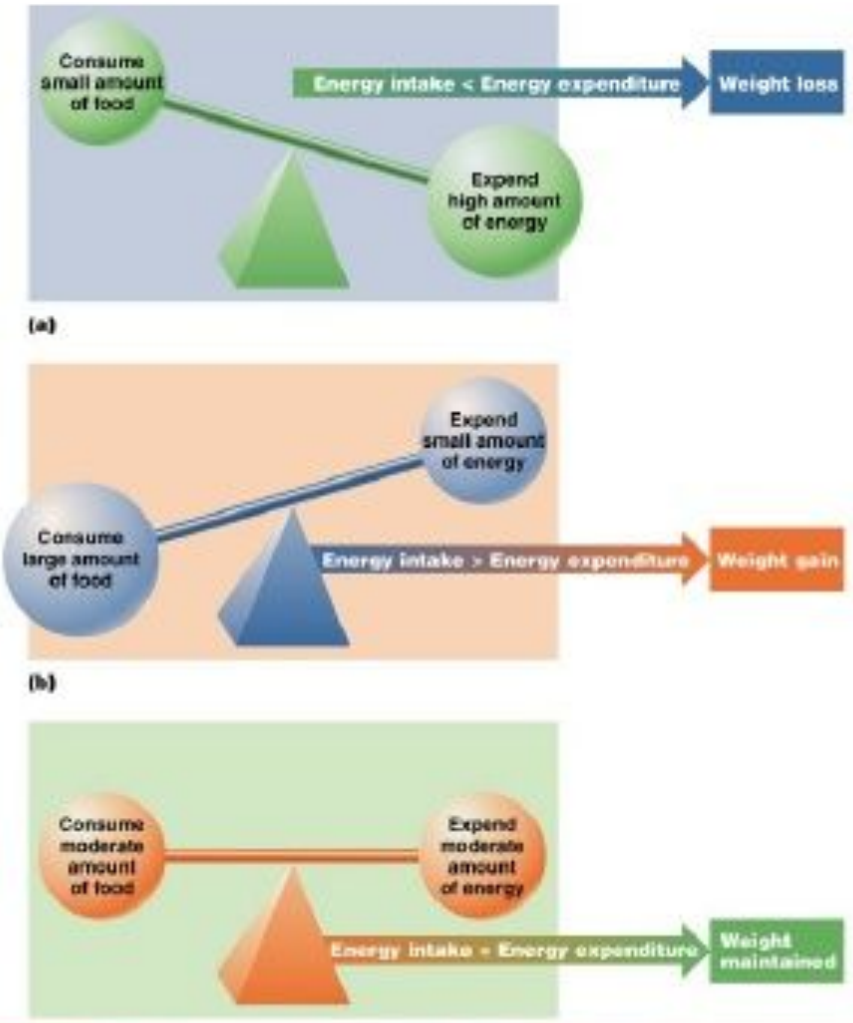


Carr MC. JCEM 88: 2404, 2003.

- Pear

Obesity

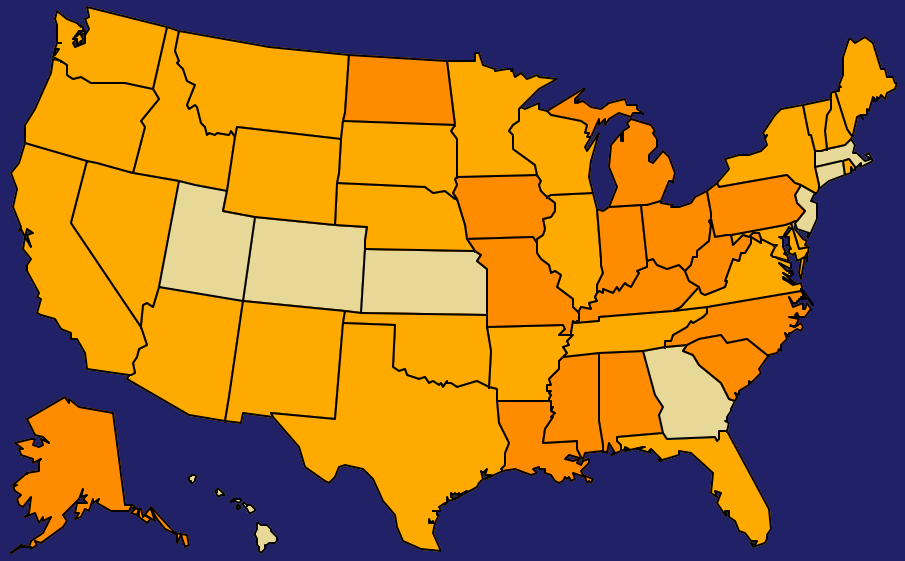
- Obesity results from an imbalance between lipogenesis (fat synthesis) and lipolysis (fat destruction).
- Lipogenesis which occurs in the liver and adipose tissue involves fatty acid synthesis followed by triglyceride synthesis.
- Differentiation of the pre-adipocytes to mature fat cells is referred to as adipogenesis and should not be confused with lipogenesis
- Body Mass Index (BMI): a measure of an adult's weight in relation to height
  Obesity: having a very high amount of body fat in relation to lean body mass, or
  Body Mass Index (BMI) of 30 or higher



Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

1996

Obesity (BMI≥30 kg/m^2)



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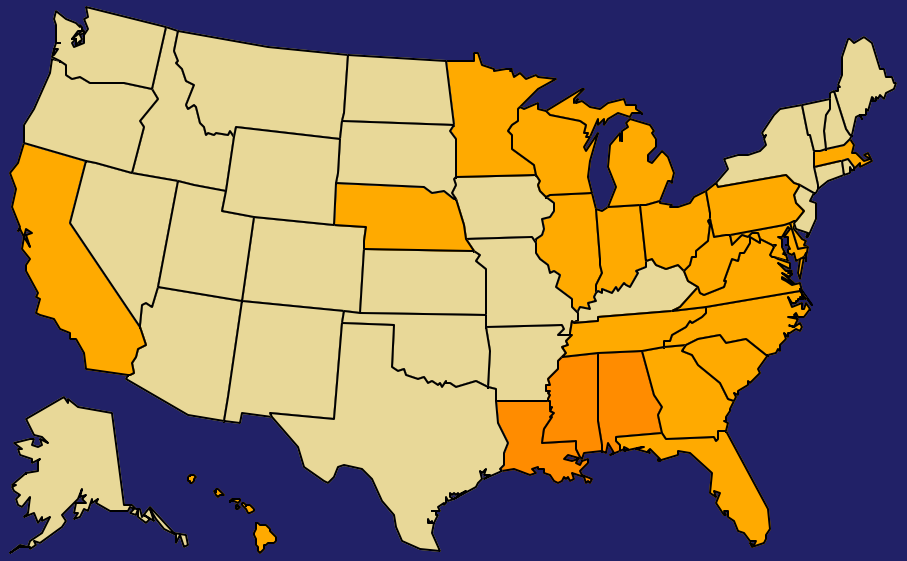
- <14.0%
- 18.0%–21.9%
- ≥26.0%

Diabetes



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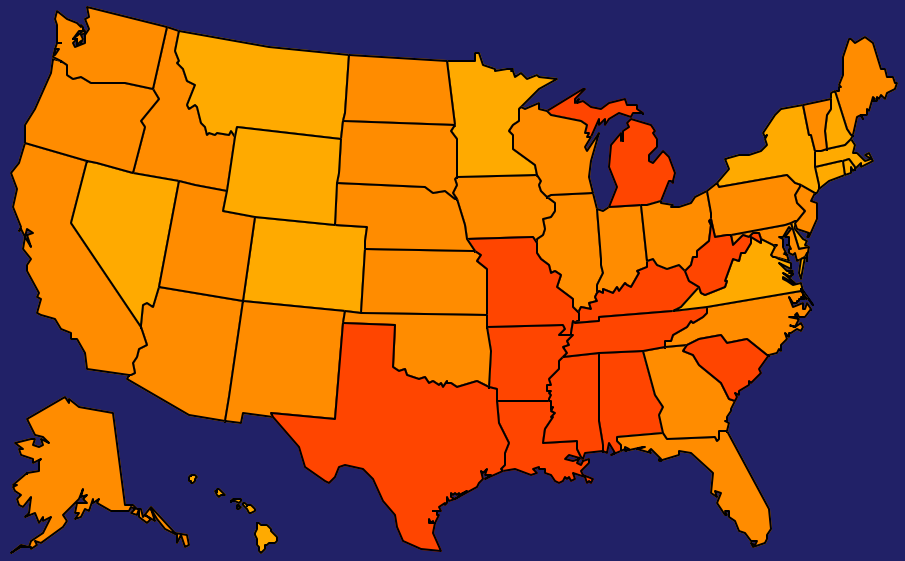
- 6.0%–7.4%
- ≥9.0%

CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2000

Obesity (BMI≥30 kg/m^2)



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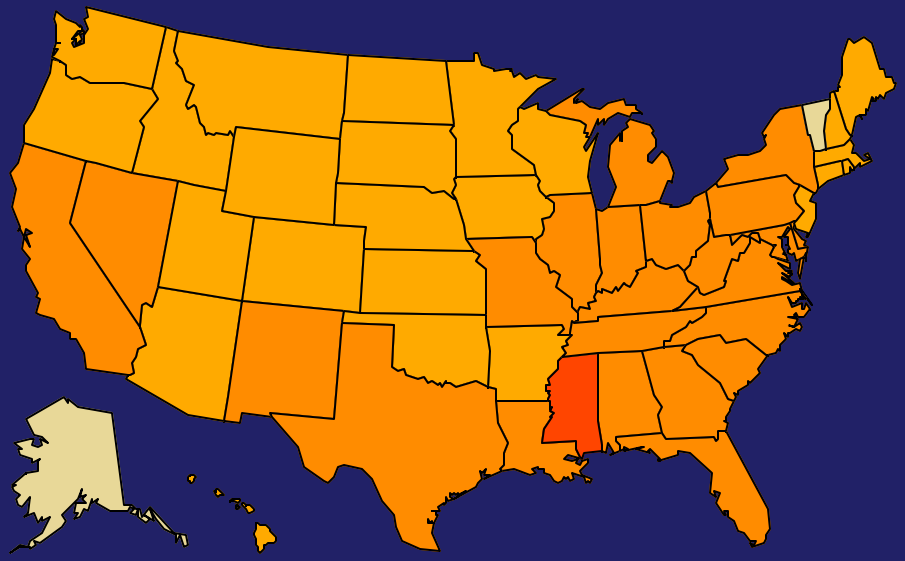
Diabetes



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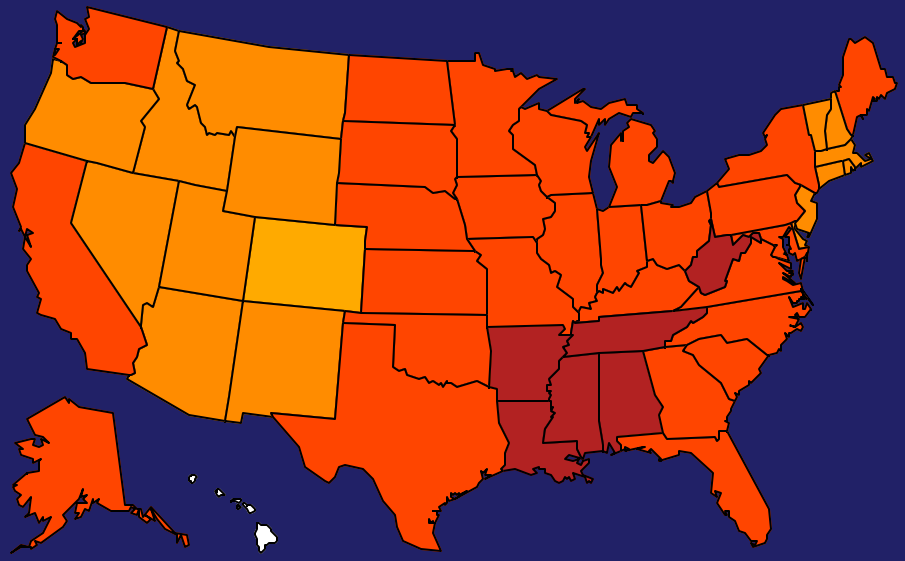
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2004

Obesity (BMI≥30 kg/m^2)



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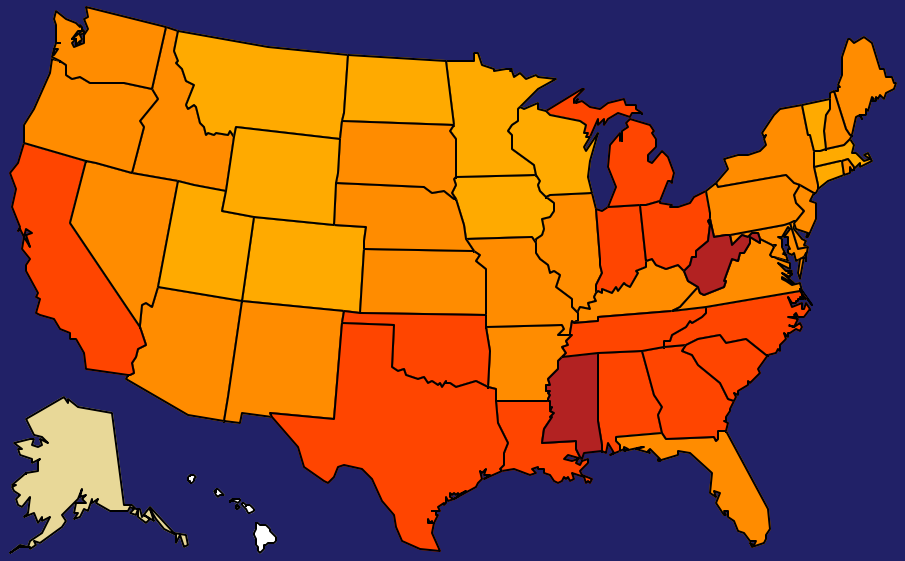
Diabetes



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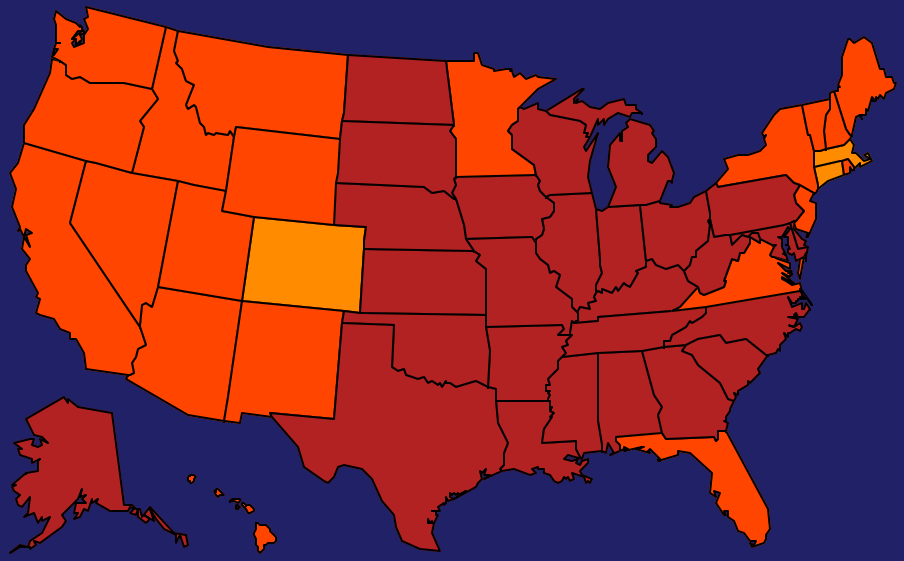
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2008

Obesity (BMI≥30 kg/m^2)



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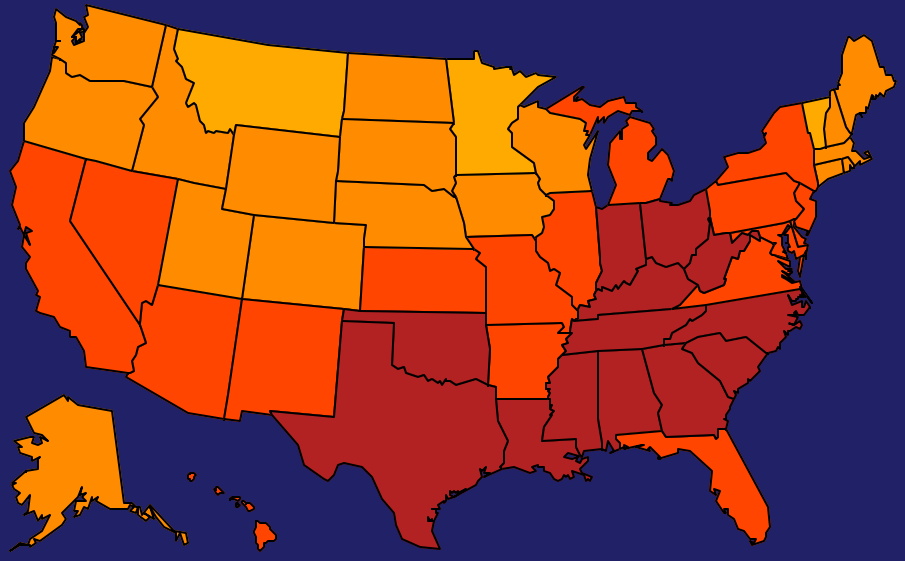
Diabetes



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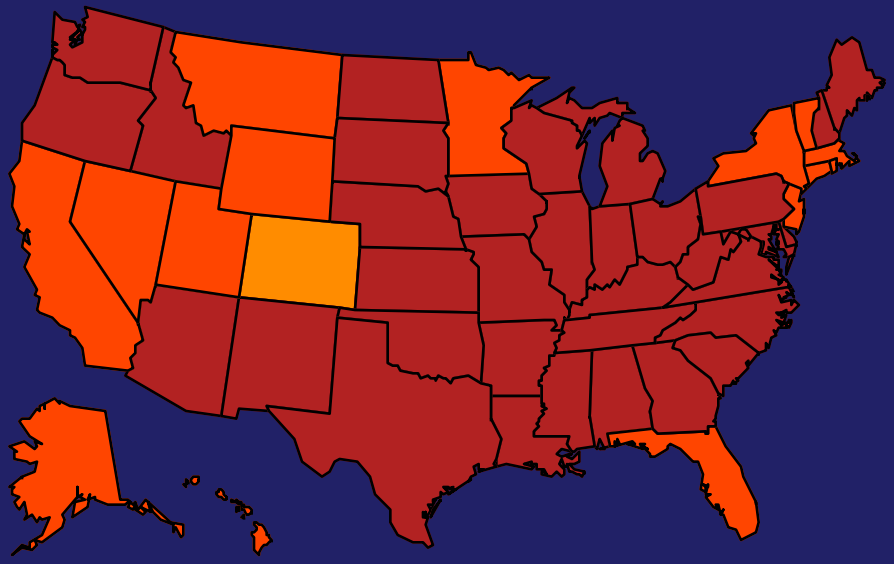
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

2012

Obesity (BMI≥30 kg/m^2)



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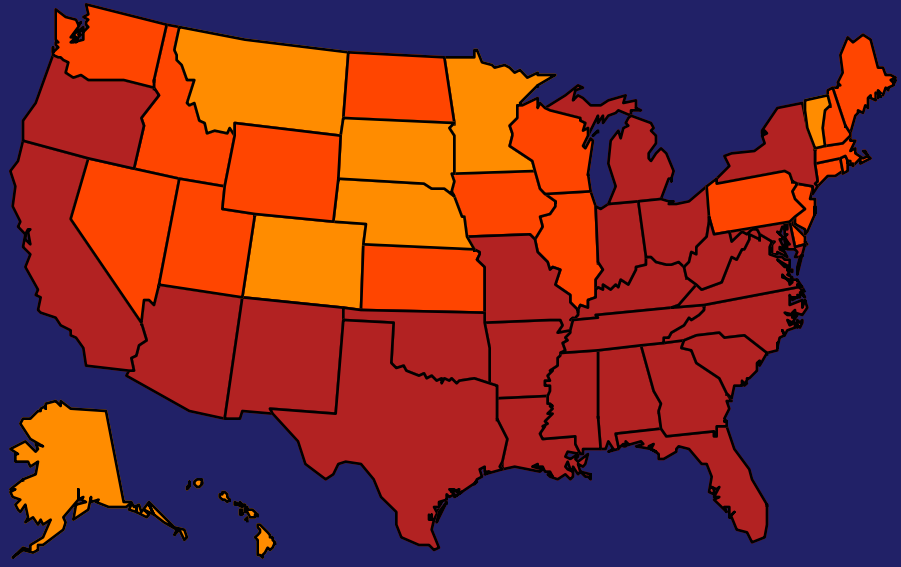
Diabetes



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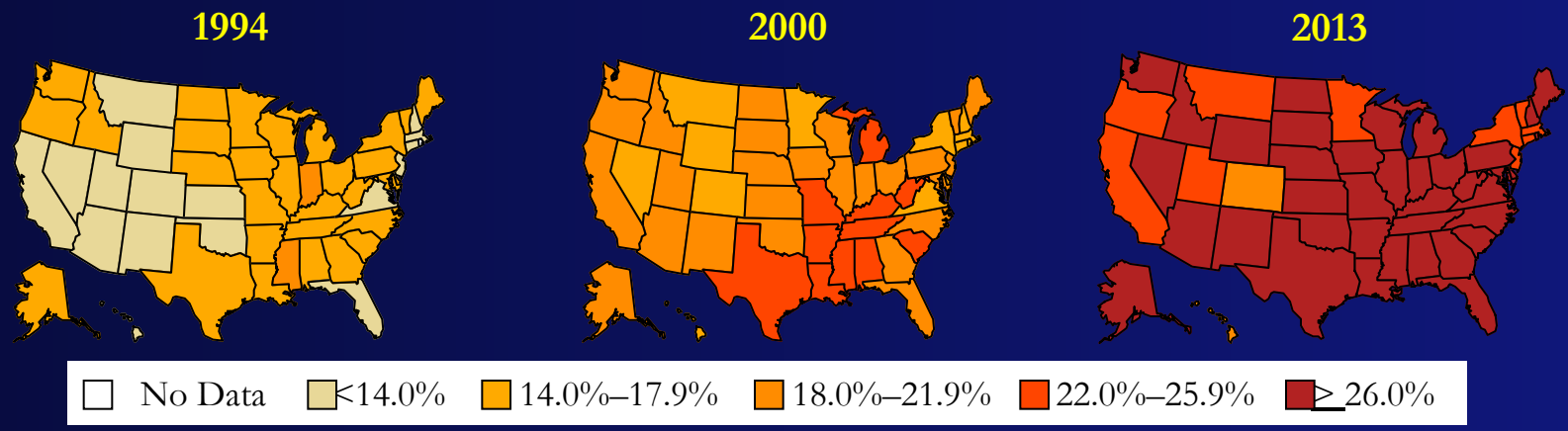
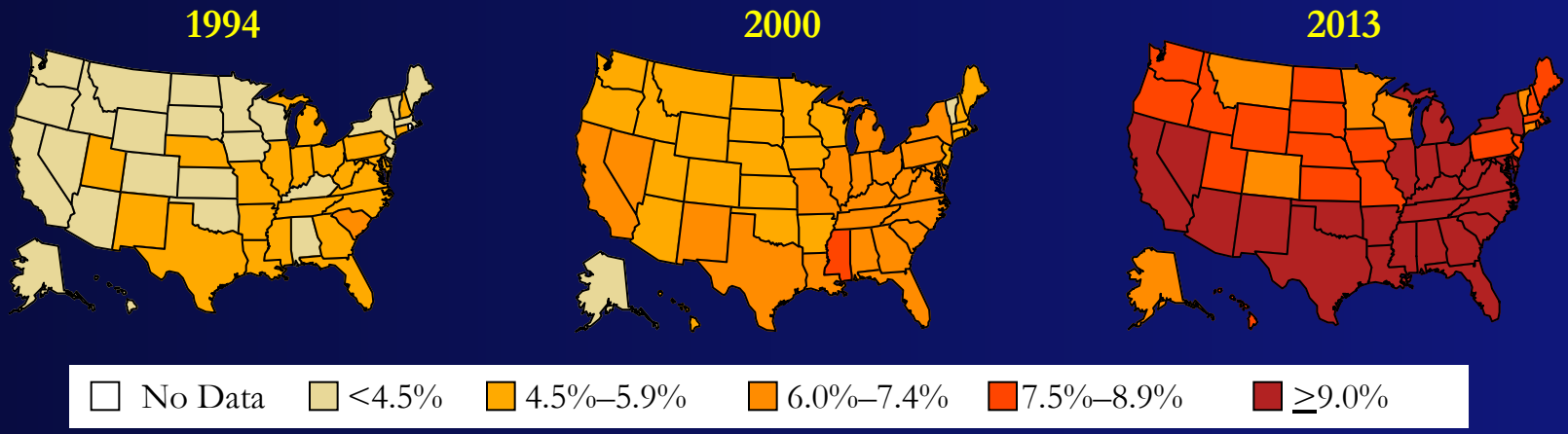
CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥30 kg/m^2)



Diabetes

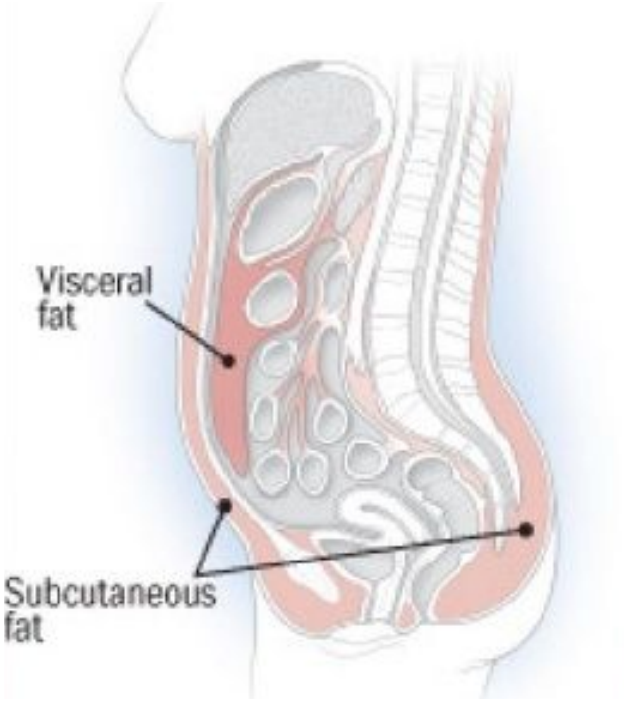


CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Anatomical Features

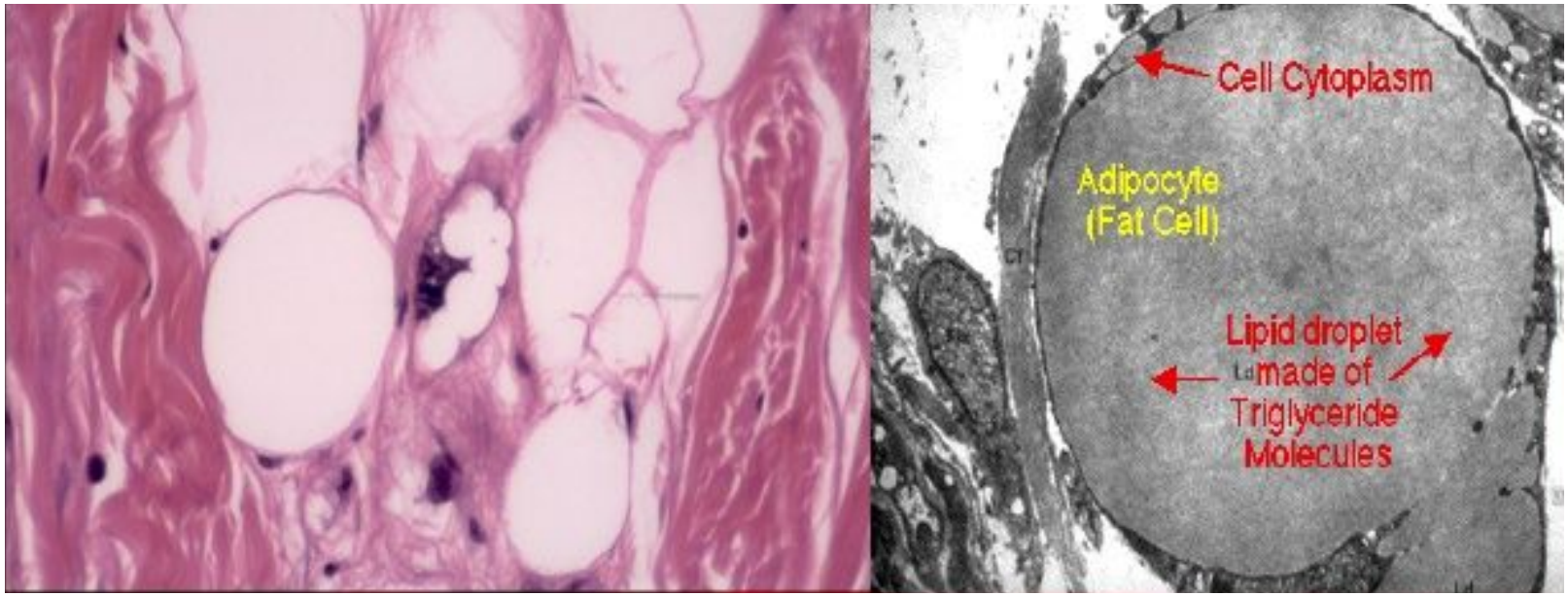
- In humans, adipose tissue is located beneath the skin (subcutaneous fat), and is found around internal organs (visceral fat).

- Adipose tissue found in specific locations - referred to as ‘adipose depots’



Adipose Tissue

- Adipose tissue or fat is loose connective tissue composed of adipocytes. Its main role is to store energy in the form of fat, although it also cushions and insulates the body.

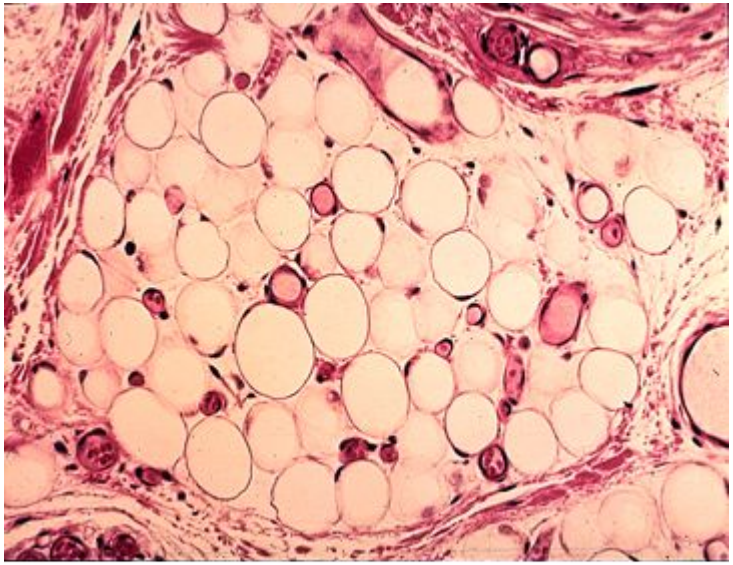


Adipose Tissue

Uniocular (white) Fat

Male
greater omentum
(pot belly)

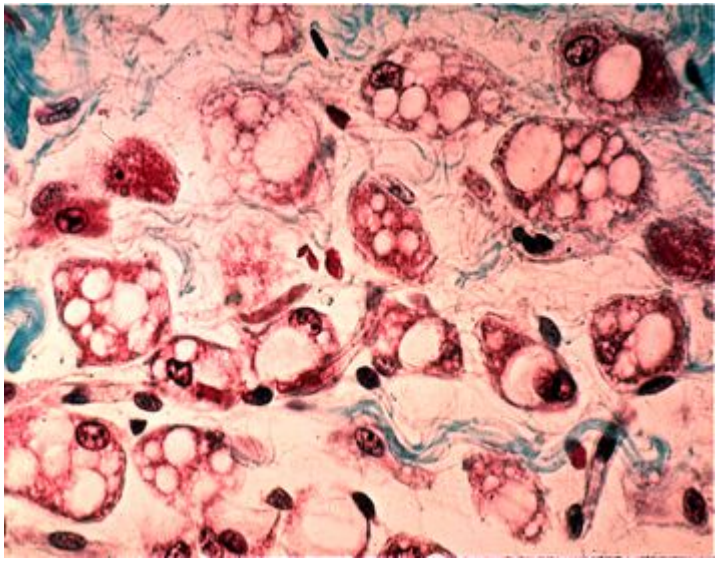
Female
buttocks, thighs
breasts



Multiocular (brown) Fat

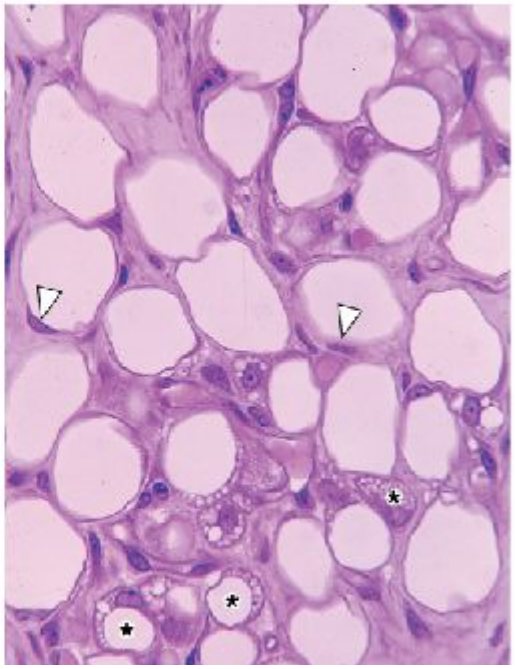
Hibernating animals

developing fat - babies



WAT Adipocyte Features

- White uniocular cells
  - Large lipid droplets surround by thin cytoplasm
  - Flattened, eccentric nuclei
  - ~ 0.1 mm in diameter
  - Fat stored as triglycerides and cholesterol esters
  - Secretes adipocytokines – leptin, resitin, etc



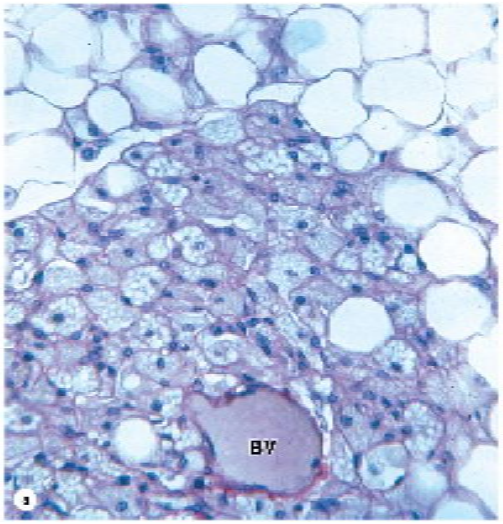
- White (20-25% of total body weight)

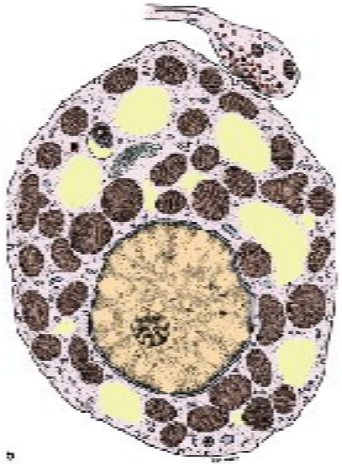
- Superficial depot (subcutaneous)
- Visceral fat depots (peri-renal, mesenteric)
- Bone marrow, breast tissue

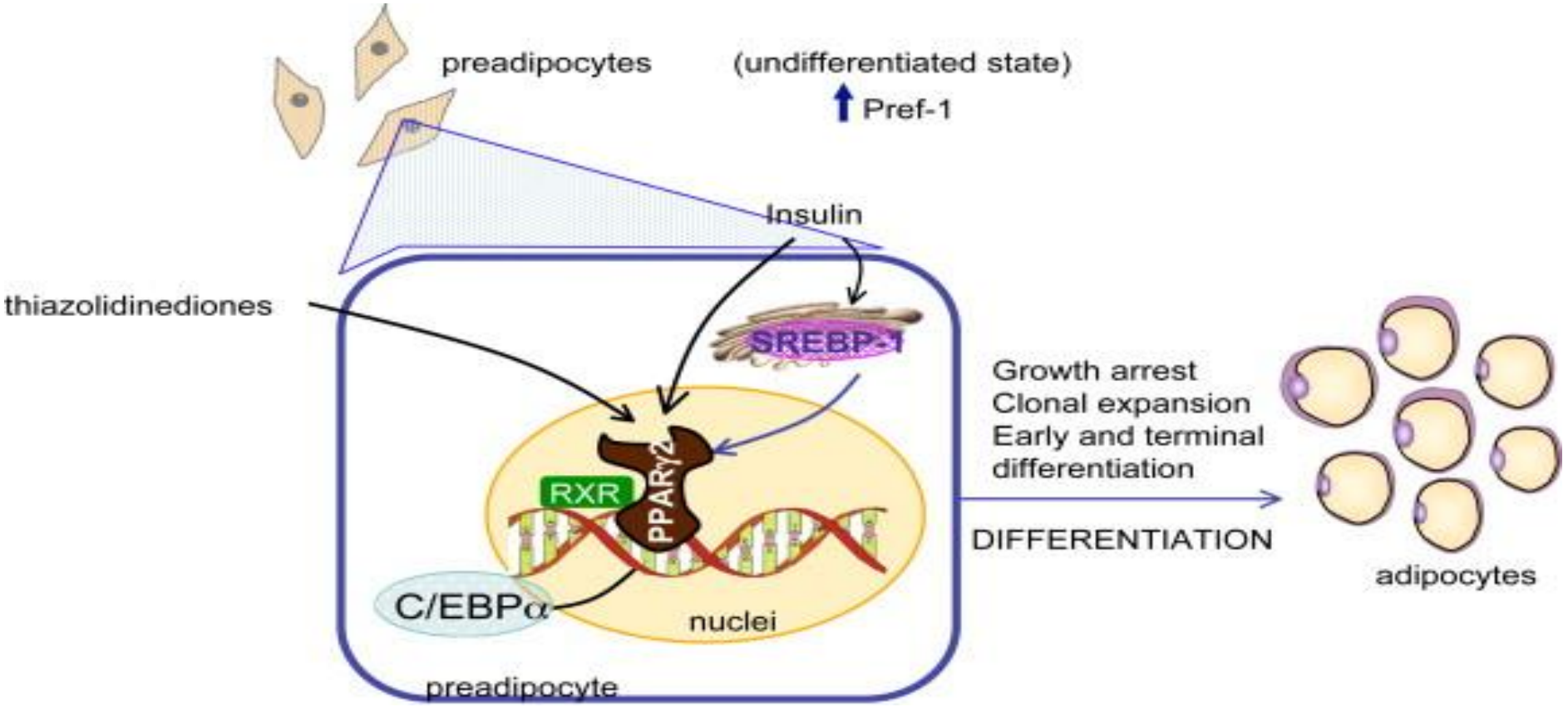
- Hormone responsive to:
  - Insulin
  - glucocortidcoids,
  - Growth hormone
  - Noradrenaline

Brown Adipose Tissue

- Multiocular Cells
- Polygonal shape
- Considerable cytoplasm
- Scattered lipid droplets
- Round central nucleus
- Brown color from mitochondria
- Used to generate heat



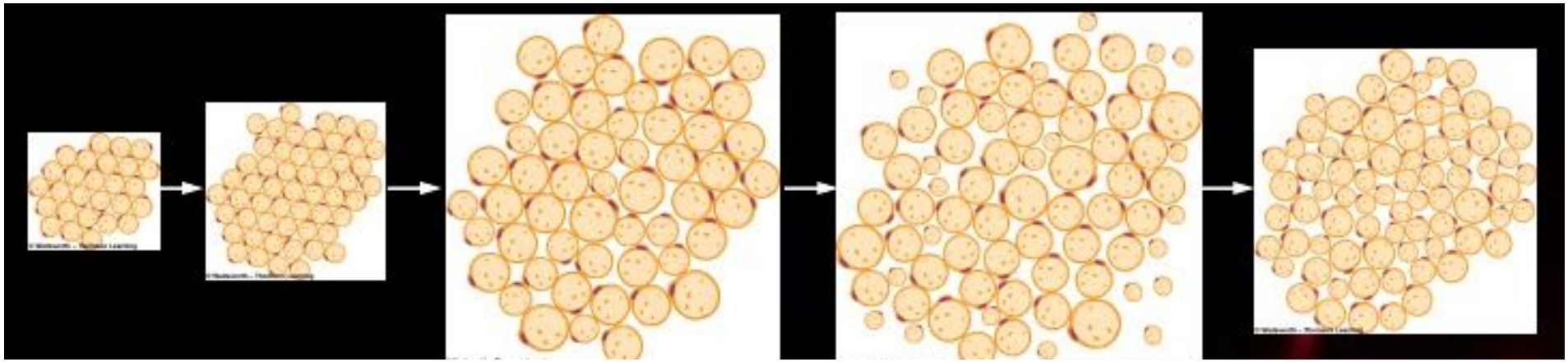




Adipogenesis. Formation of mature adipocytes containing a lipid vesicle from preadipocytes by a differentiation process regulated by the transcription factor PPAR?. This factor is activated by the transcription factors C/EBP and SREBP-1.

Archives of Medical Research Volume 39, Issue 8 2008 715 - 728

Fat Cell Development



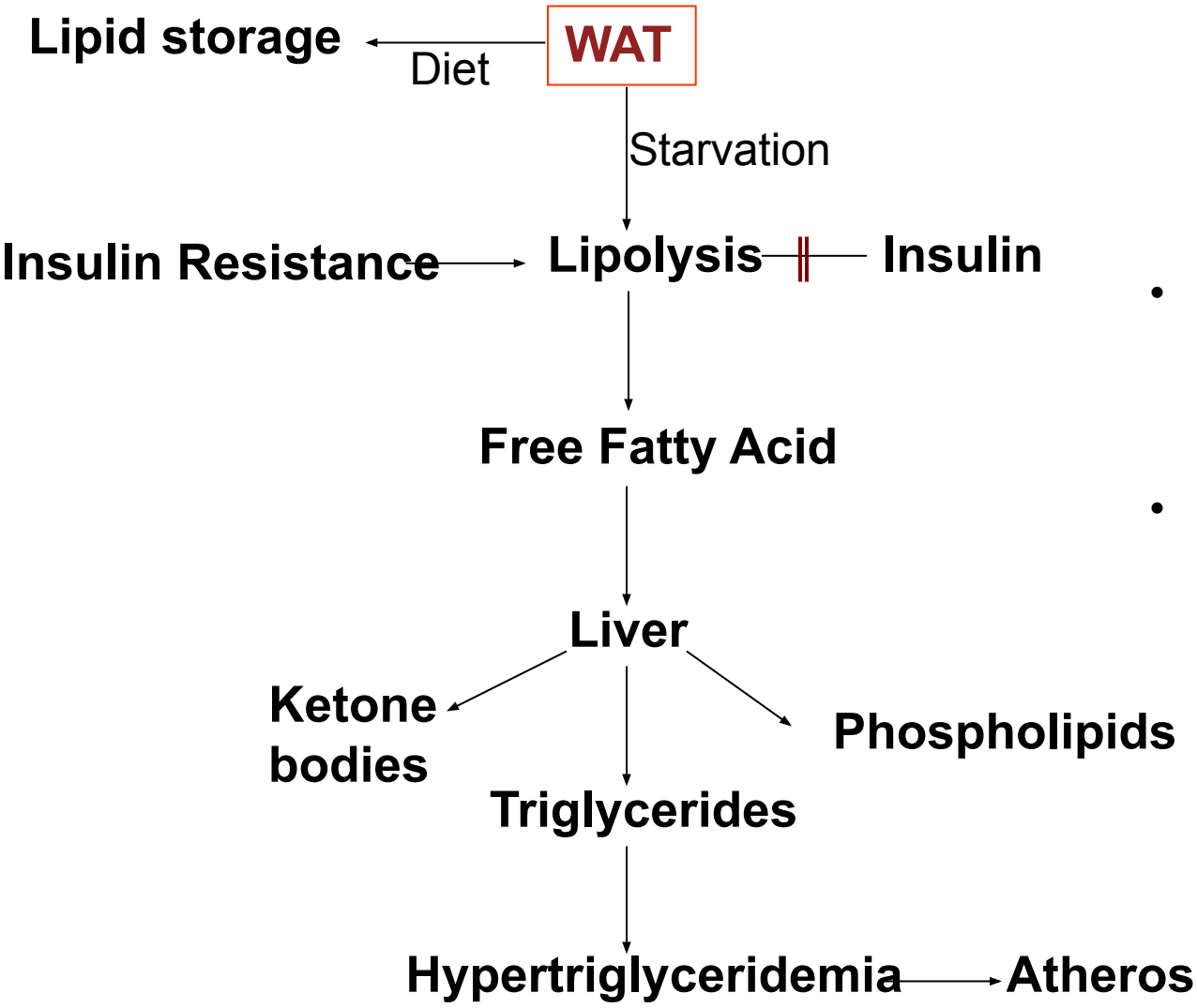
During growth, fat cells increase in number

As energy intake exceeds expenditure, fat cells increase size.

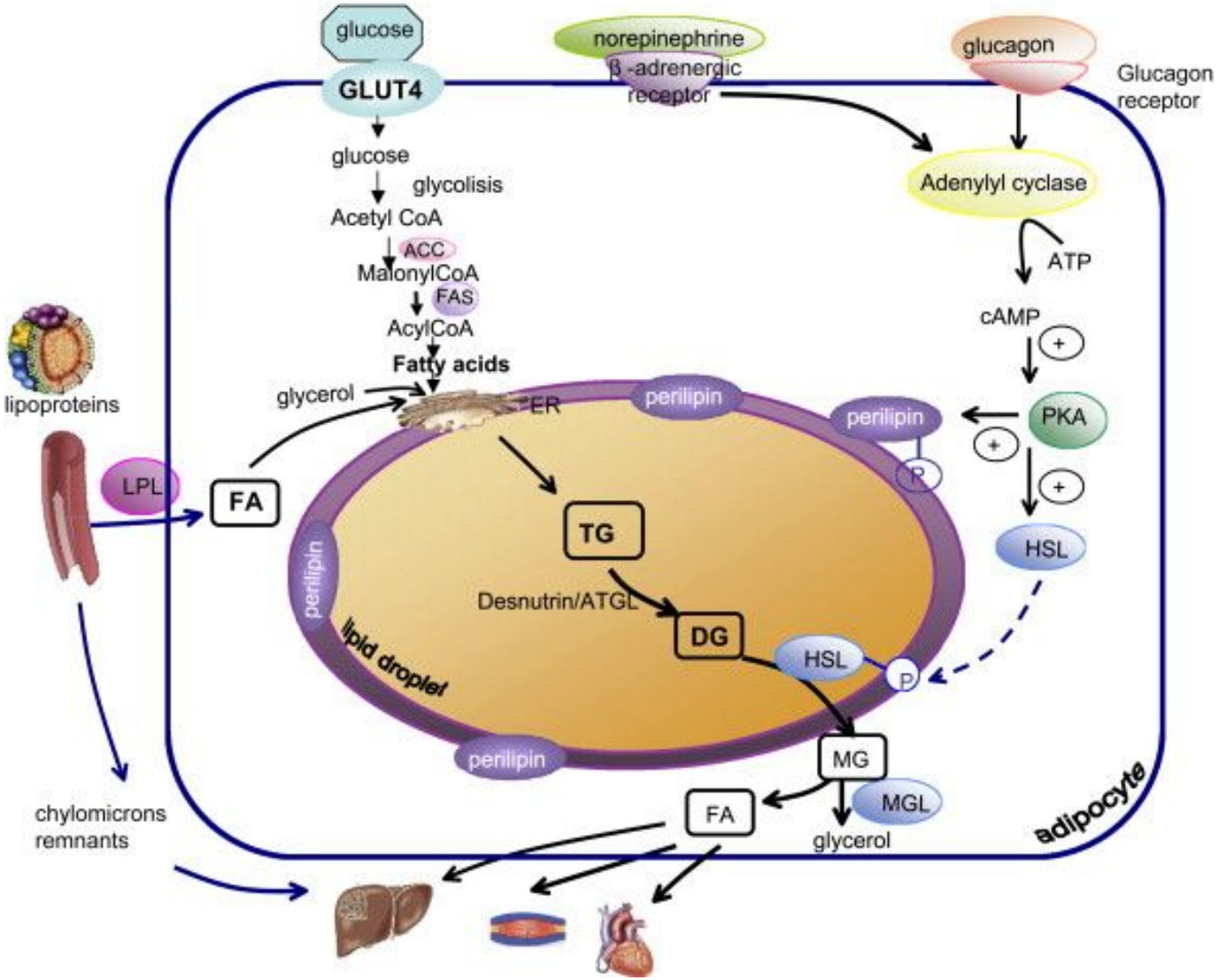
After cell enlarge and energy intake continues to exceed expenditure, cells increase in number again.

With fat loss, size of the cells shrink, but not number

Control of Release of FFA From White Adipose Tissue

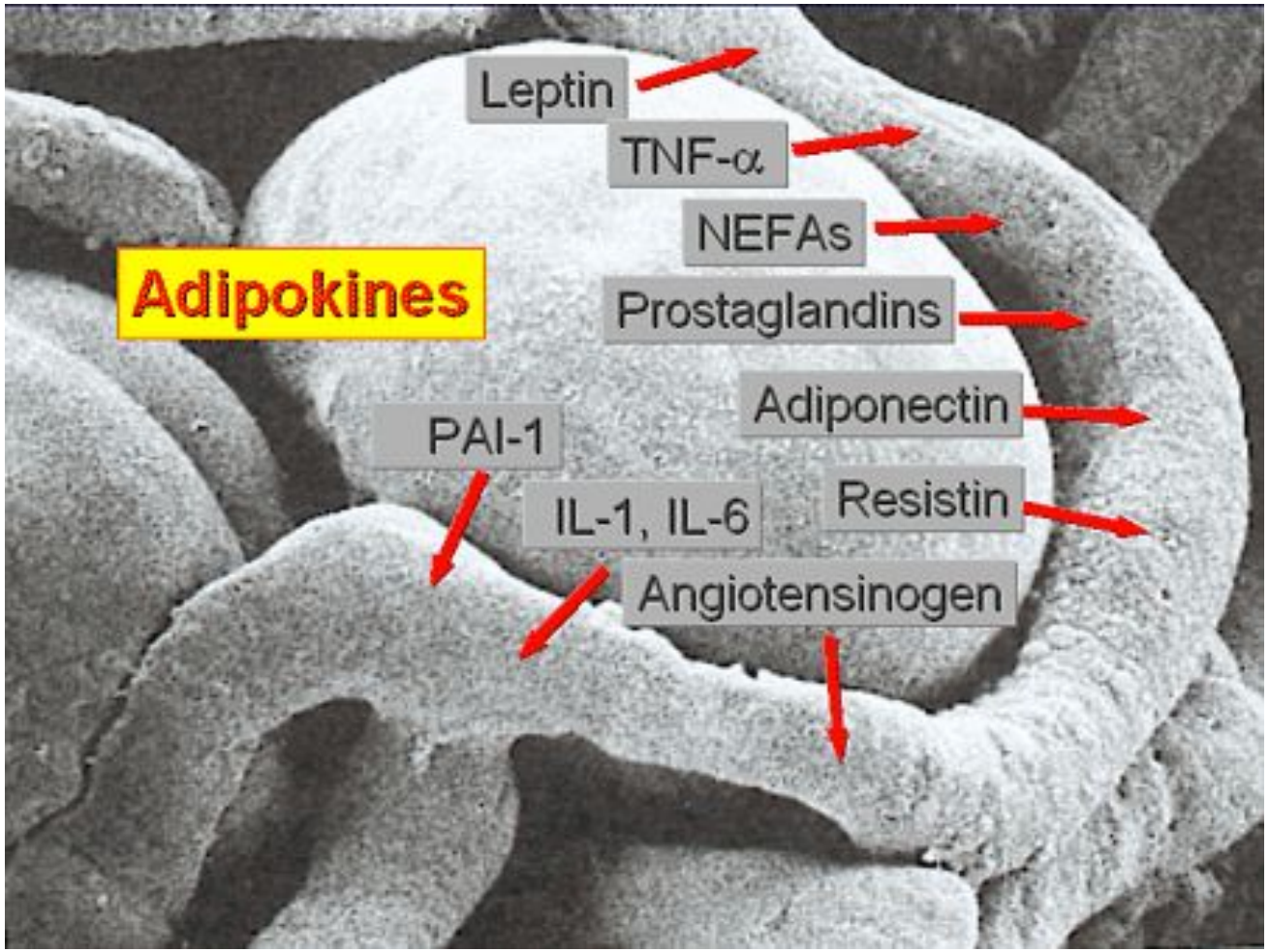


- Adipose tissue serves as a buffer for FFA levels following feeding (similar to the way liver buffers blood glucose levels)
- FFA are released from WAT when systemic energy needs are not being met
- FFA levels are a predictor of future development of type 2 diabetes

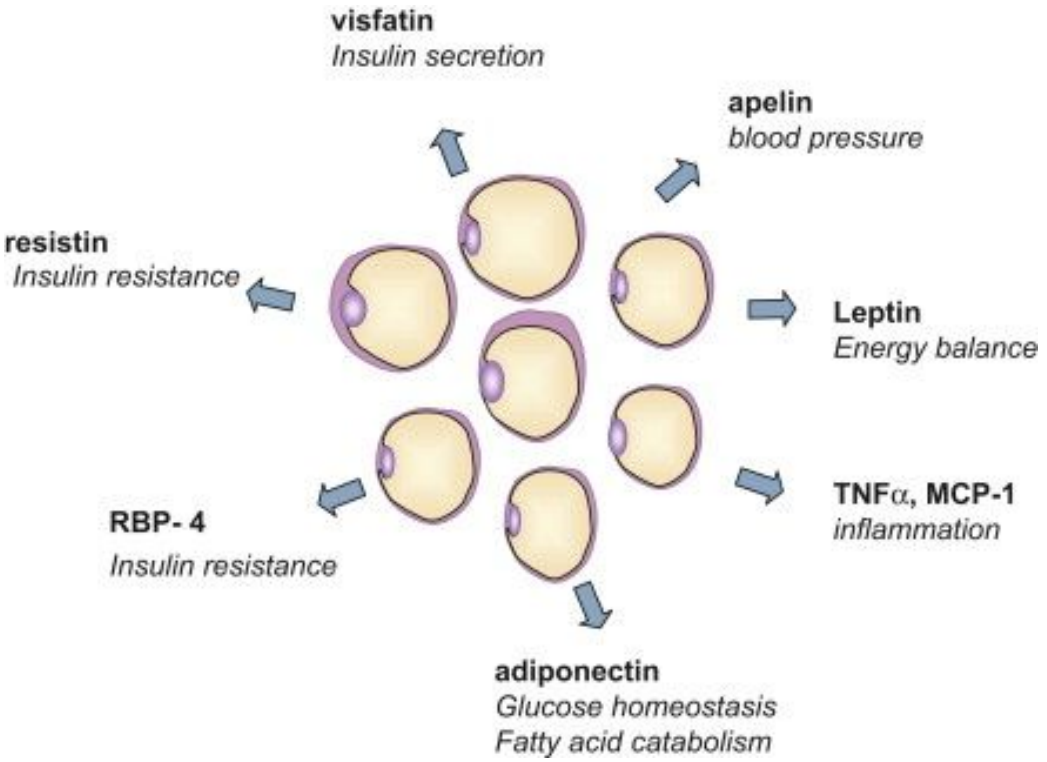


Lipogenesis and lipolysis. Glucose excess is oxidized via glycolysis to acetyl-CoA in the adipocyte and then converted into acyl-CoA, which are then esterified in the endoplasmic reticulum (ER) to triglycerides (TG). These are then translocated into the lipid droplet. Fatty acids (FA) obtained from lipoproteins are also esterified into TG and stored. Under fasting conditions, lipolysis is activated by G-protein-coupled receptors resulting in an increase in cAMP that phosphorylates the protein perilipin located in the membrane of the lipid droplet. cAMP also phosphorylates the hormone-sensitive lipase (HSL) that triggers its translocation from the cytoplasm to the lipid droplet and induces with highest specific activity the hydrolysis of diglycerides produced by the adipocyte triglyceride lipase (ATGL) to form monoglycerides (MG). MG are then released to nonadipose tissues, mainly for energy purposes.

Adipokines


Adipokines
Leptin
TNF-α
NEFAs
Prostaglandins
Adiponectin
Resistin
PAI-1
IL-1, IL-6
Angiotensinogen

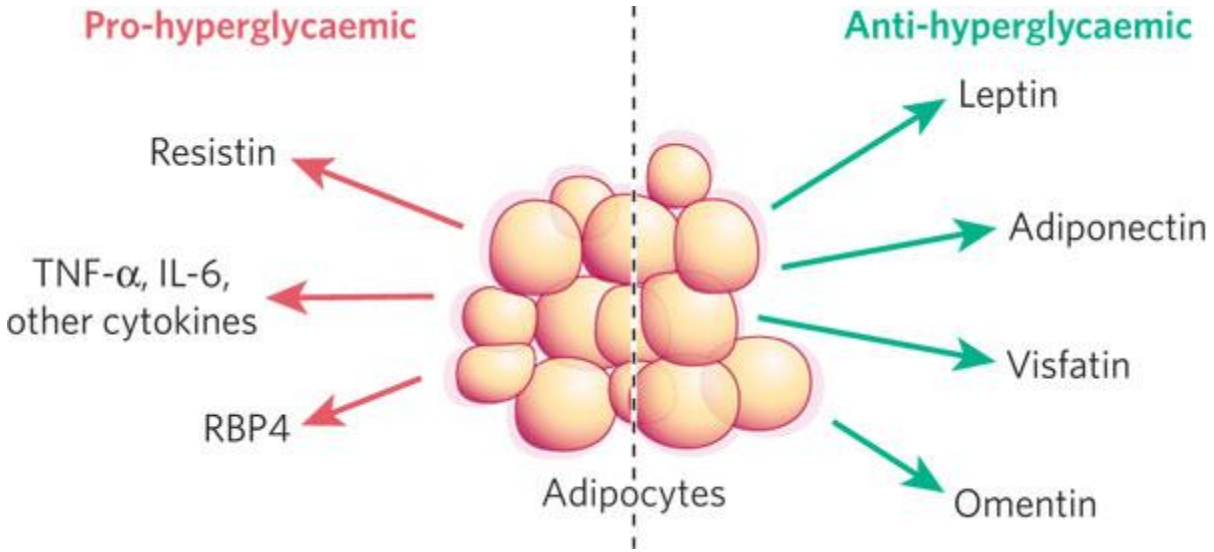
Adipose tissue as endocrine organ

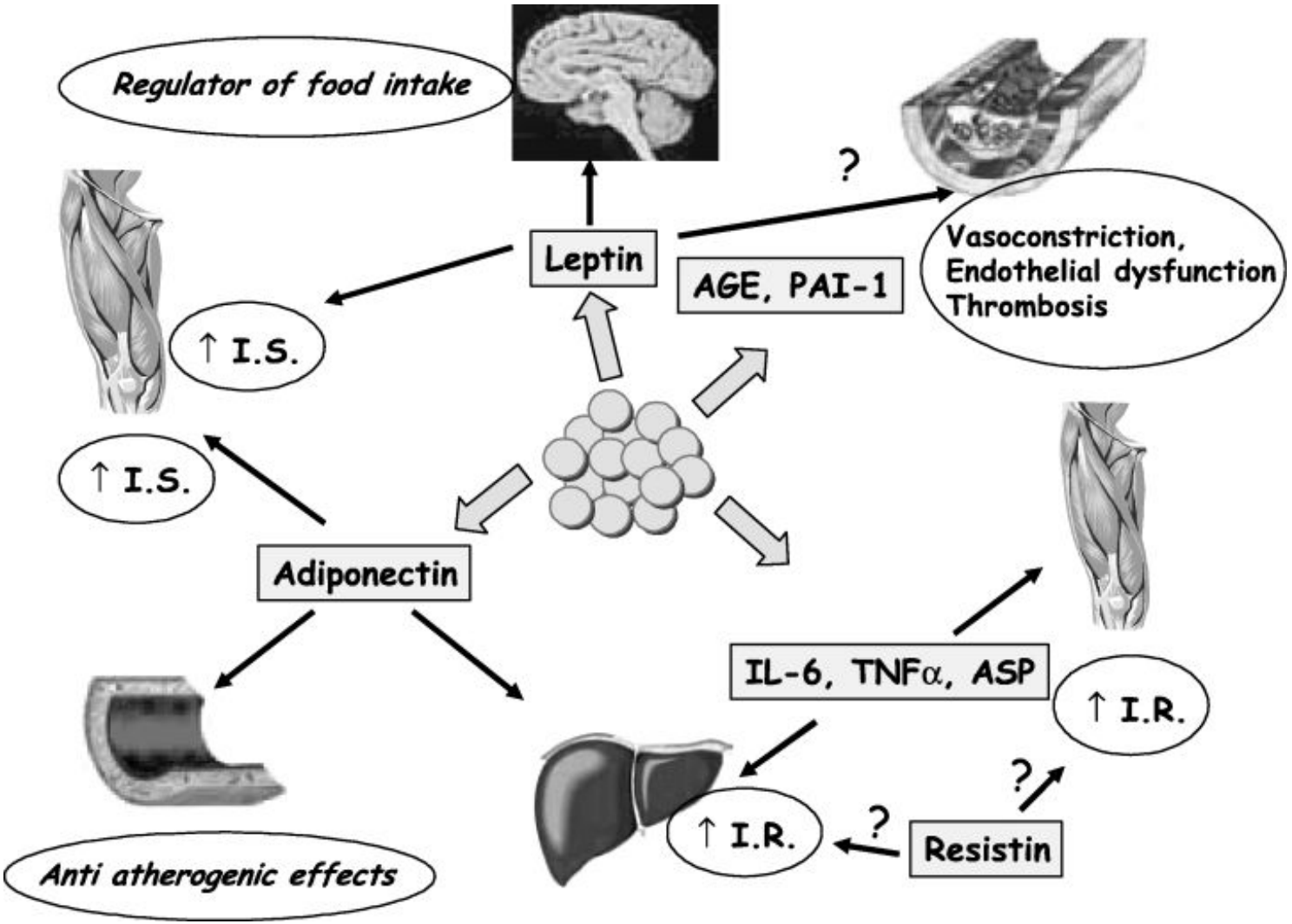


Adipocytes secrete several proteins with endocrine functions designated as adipokines that regulate glucose and fatty metabolism in peripheral tissues, energy expenditure homeostasis, inflammatory response, and blood pressure, among others. Imbalanced secretion of some of these adipokines is associated with obesity and metabolic syndrome.

Adipokines

- Vascular Disease Related
  - Angiotensinogen
  - PAI-1
- Insulin Resistance Related
  - ASP (Acylation-stimulating protein)
  - TNFa
  - IL-6
  - Resistin
  - Leptin
  - Adiponectin



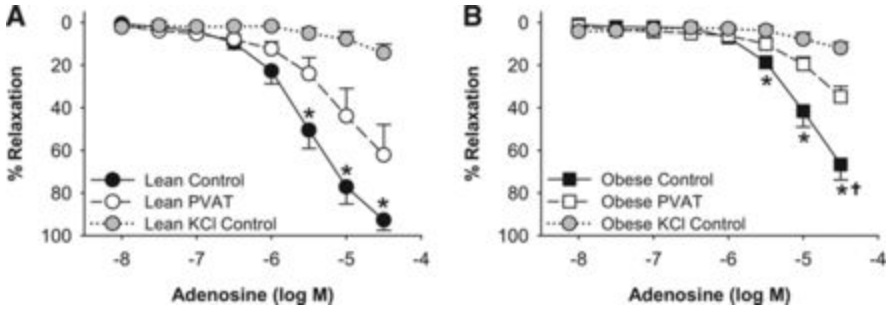


Adipokines implicated in energy homeostasis, insulin sensitivity (IS), insulin resistance (IR) and atherogenesis. Excessive production of interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), acylation-stimulating protein (ASP) deteriorates insulin action in muscle and/or in liver, whereas increased angiotensin (AGE) and PAI-1 secretion favors hypertension, endothelial dysfunction and thrombosis. The role of resistin on insulin resistance is still not clear. Leptin regulates energy balance and exerts an insulin sensitizing effect. Adiponectin increases insulin action in muscle and liver and exerts an anti atherogenic effect.

Ronti et al., 2006

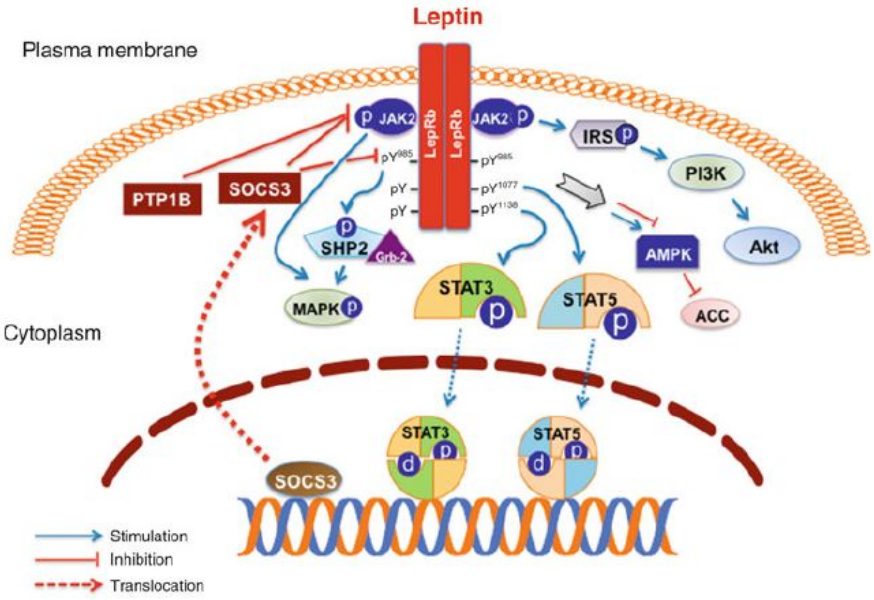
Effects of Adipose on Adenosine Induced Relaxation in Porcine Coronary Arteries

- Perviascular adipose tissue (PVAT) was removed from Porcine coronary arteries
- Arteries were preconstricted and then given adenosine to induce relaxation.
- The PVAT was then reintroduced in a floating bath and relaxation was again examined
  - Results: PVAT in both lean and obese Pigs reduced relaxation



Leptin

- A 16 kDa polypeptide product of the obese (ob) gene.
- Leptin, expressed and secreted primarily by adipocytes, acts via a family of receptor (OB-R) isoforms to mediate an ever growing wide range of physiological effects.
- These receptors have divergent signaling capabilities, regulating pathways which include JAK/STATS and MAP kinases.
- Its expression is influenced by energy stores in fat.
- Leptin levels increase within hours of a meal in rodents and after several days of overfeeding in humans
- Insulin stimulates leptin expression and secretin in primary adipocytes
- Other factors, such as dexamethasone, TNF-alpha and IL-6 regulate its release.



Physiological effects of Leptin

- Regulation of food intake, energy expenditure and body weight.
  - Absence leads to uncontrolled food intake obesity
- Thermogenesis
- Reproductive functions
- Direct effects on liver and muscle cells
- Related to inflammatory response

Leptin

- Concentrations in the blood range around several ng/ml, both as an active free form and as an inactive form which occurs by its association with plasma proteins and the leptin receptor isoform.

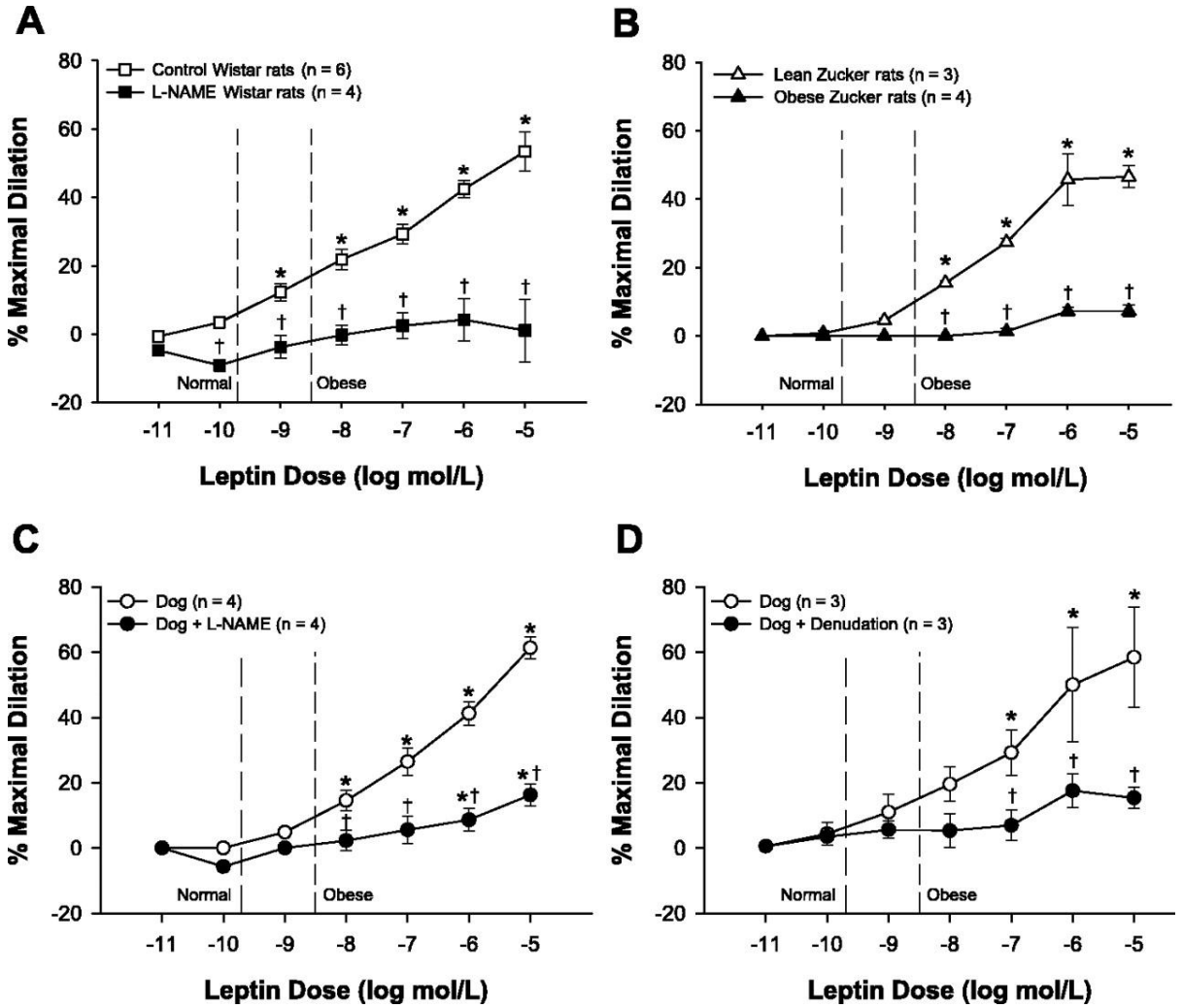
- Leptin Receptors (OB-R) – expressed in a variety of tissues, suggesting that it has a wide range of actions.

- However, leptin receptor mutations cause early onset obesity in rodents. This is consistent with measurements of high leptin concentrations and low leptin receptor expression in most diabetic patients.

Role of leptin in lipid metabolism

- Leptin activated lipid oxidation by inducing the expression of enzymes involved in lipid metabolism
- Activate AMP-activated protein Kinase (AMPK)
- Inhibits acetyl coenzyme-A carboxylase (ACC)
- Increase insulin sensitivity
- Inhibits intracellular lipid concentrations
- Stimulates apoptosis of adipocytes

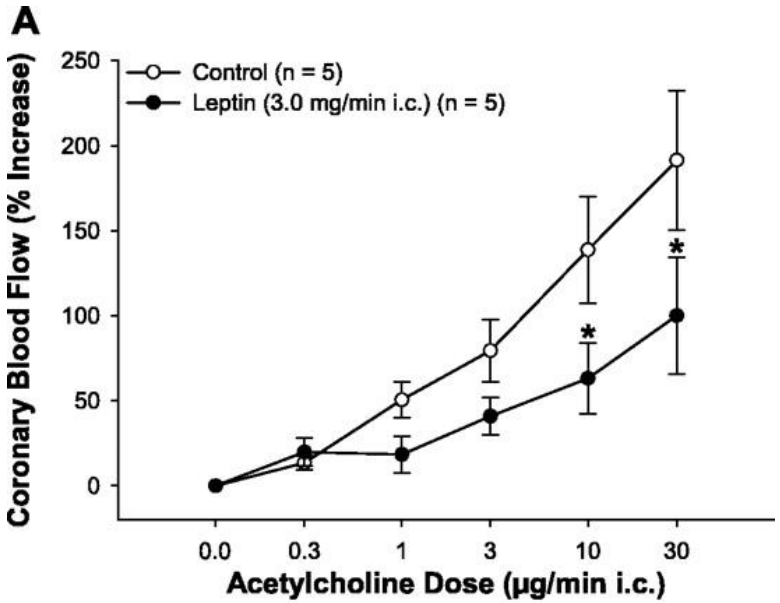
Hyperleptinemia, associated with prediabetes, is an independent risk factor for CAD and a mediator of coronary endothelial dysfunction.



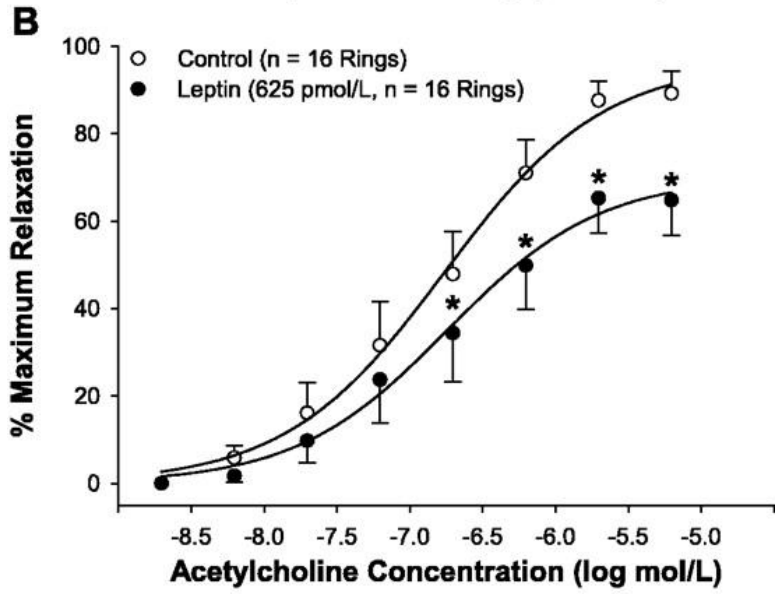
Leptin produced a concentration-dependent vasodilation in coronary arterioles isolated from Wistar rats that was abolished by treatment with Nω-nitro-l-arginine methyl ester (l-NAME)

Knudson J D et al. Am J Physiol Heart Circ Physiol 2005;289:H48-H56

Leptin impairs coronary endothelial-dependent vasodilation to acetylcholine in isolated coronary artery rings (B) and in anesthetized open-chest dogs (A).



Obese concentrations of leptin significantly attenuated coronary vasodilation to intracoronarily administered acetylcholine.



Demonstrate that acutely raising the leptin concentration to levels comparable with those observed in human obesity significantly attenuates coronary dilation/relaxation to acetylcholine (ACh) both in vivo in anesthetized dogs and in vitro in isolated canine coronary rings.

Knudson J D et al. Am J Physiol Heart Circ Physiol 2005;289:H48-H56

Leptin Resistance

- Ability of leptin to decrease body fat content suggests leptin is an anti-obesity hormone!!!!

- However, high leptin levels have been found in obese and diabetic mice and humans leptin resistance. Sometimes it is combined with low-level expression of leptin receptors.

- Other mechanisms are:
  - Mutation of the gene for leptin receptors in the brain
    - A frameshift/premature stop mutation,…c.398delG (Deta 133G mutation) causes a congenital leptin deficiency and leads to severe early-onset obesity.
    - A homozygous frameshift mutation in the human leptin (ob) gene was associated with undetectable serum leptin and extreme obesity.
  - Post receptor abnormalities in leptin signal transduction
- Impaired leptin transport across the blood-brain barrier.

- Disruption of leptin action is thought to play a role in development of diabetes. This hypotheses is supported by data showing that mutations in the ob gene cause early onset obesity and type II diabetes in mice and humans.

Effects of Leptin on Vascular Homeostasis and the Metabolic Syndrome of Insulin Resistance

Adipokines	Vascular action	Insulin action and resistance
Leptin	↑ NO by increasing eNOS production ↑ ET-1 ↑ proliferation and migration of EC and VSMC ↑ ROS accumulation and oxidative stress ↑ VSMC apoptosis ↑ angiogenesis ↑ release of monocyte colony-stimulating factor ↑ cholesterol accumulation under hyperglycemia	↑ glucose transport Reverses insulin resistance in lipodystrophy ↑ sympathetic tone ↑ blood pressure

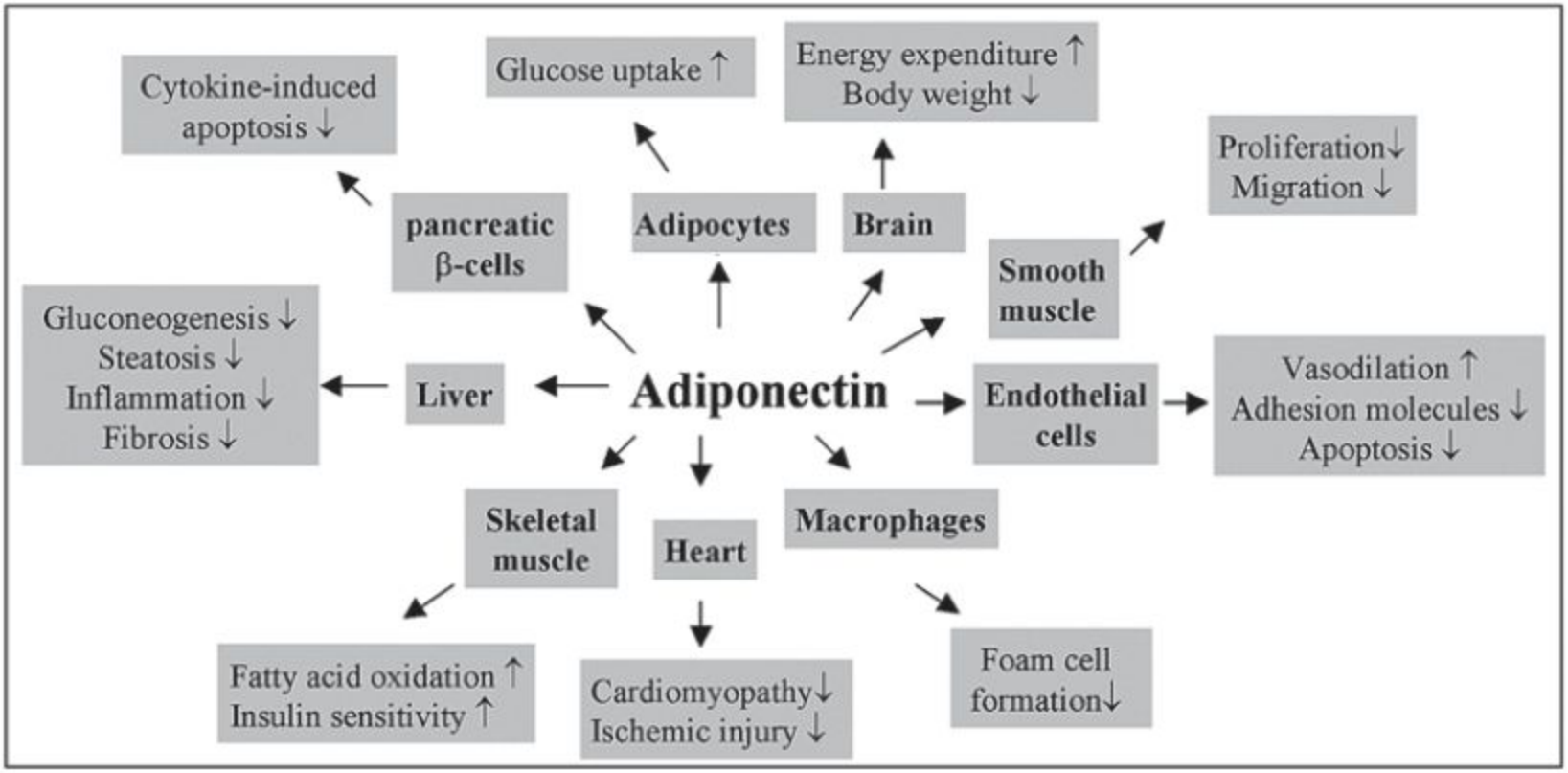
Adiponectin

- What is adiponectin?
  - Collagen-like protein secreted by adipocytes
  - physiological role not fully established
  - proposed to have:
    - anti-atherogenic properties
    - anti-inflammatory properties
    - insulin sensitizing properties

- A peptide hormone made by adipocytes in response to high fat reserves:
  - Increases FA uptake by myocytes and the rate of FA oxidation.
  - Slows FA synthesis in the liver
  - Slows gluconeogenesis in the liver
  - Acts through AMPK

- Humans who are obese or suffer from Type II diabetes show reduced levels of adiponectin

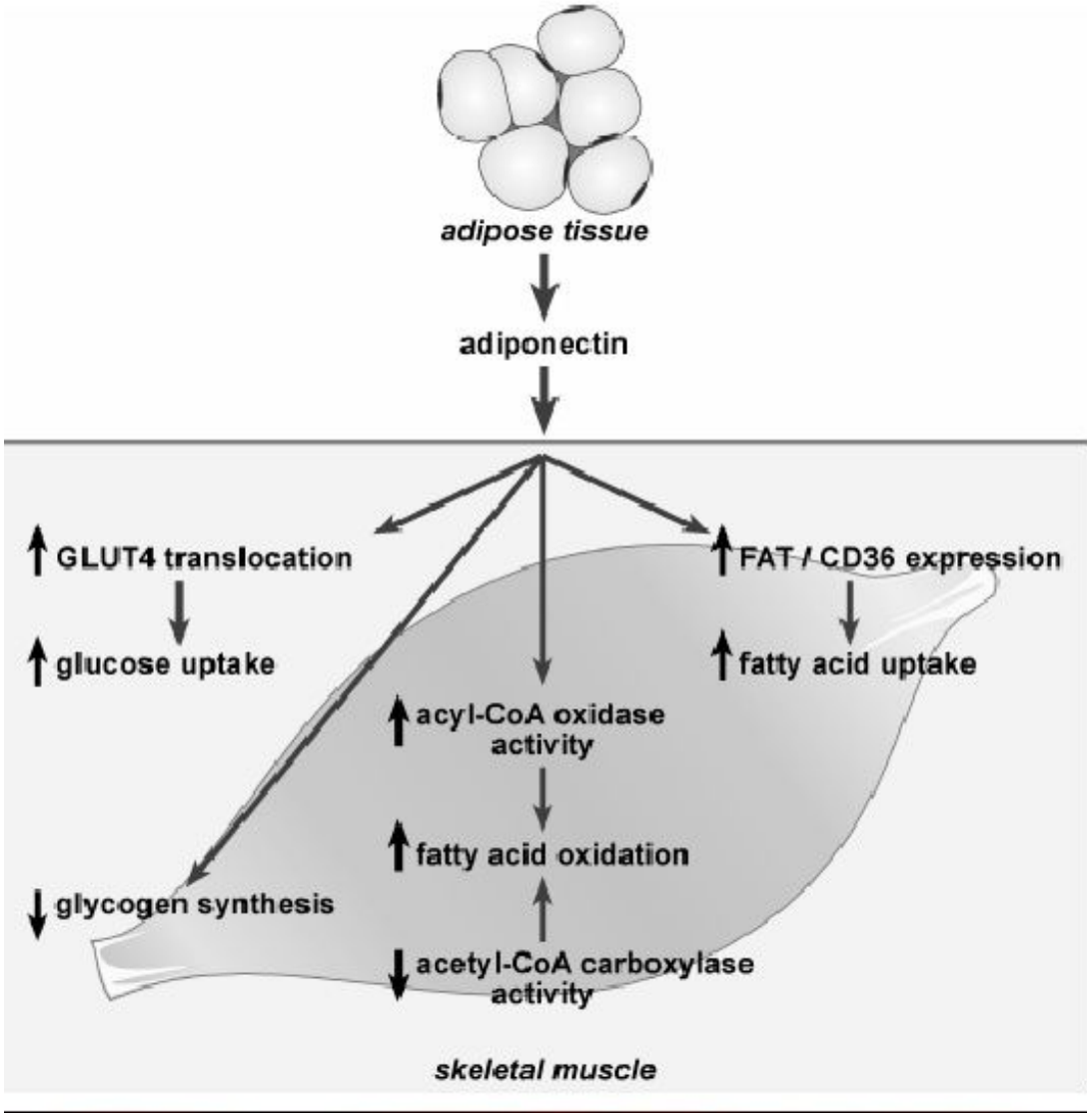
- Thiazolidinediones used to treat Type II diabetes elevate expression of adiponectin


Cytokine-induced apoptosis ↓
Glucose uptake ↑
Energy expenditure ↑
Body weight ↓
Proliferation ↓
Migration ↓
pancreatic β-cells
Adipocytes
Brain
Smooth muscle
Gluconeogenesis ↓
Steatosis ↓
Inflammation ↓
Fibrosis ↓
Liver
Adiponectin
Endothelial cells
Vasodilation ↑
Adhesion molecules ↓
Apoptosis ↓
Skeletal muscle
Heart
Macrophages
Fatty acid oxidation ↑
Insulin sensitivity ↑
Cardiomyopathy ↓
Ischemic injury ↓
Foam cell formation ↓

Adiponectin Properties

1. Lower in:
    a. Men than in women.
    b. Obese individuals with metabolic syndrome.
    c. Obese women with PCOS.
    d. Patients with type 2 diabetes.
    e. Patients with CAD.
    f. Those at risk for type 2 diabetes and first-degree relatives.
    g. Some adiponectin gene mutations associated with increased type 2 diabetes.
    h. Diabetes-susceptibility locus mapped to chromosome 3q27, site of adiponectin gene.
2. Higher levels are protective for type 2 diabetes.
3. Positively correlates with insulin sensitivity (independent of age, BP, adiposity, lipids) and HDL-C in patients with and without type 2 diabetes.
4. Inversely relates to degree of adiposity (BMI, fat mass), glucose, insulin, TG levels, systolic BP, intramuscular fat content, CRP, TNF-α, IL-6, and endothelin.
5. Increased with weight loss (most studies) and glitazone therapy .
6. Not increased with exercise.

Role of Adiponectin in the Regulation of Carbohydrate and Lipid Metabolism

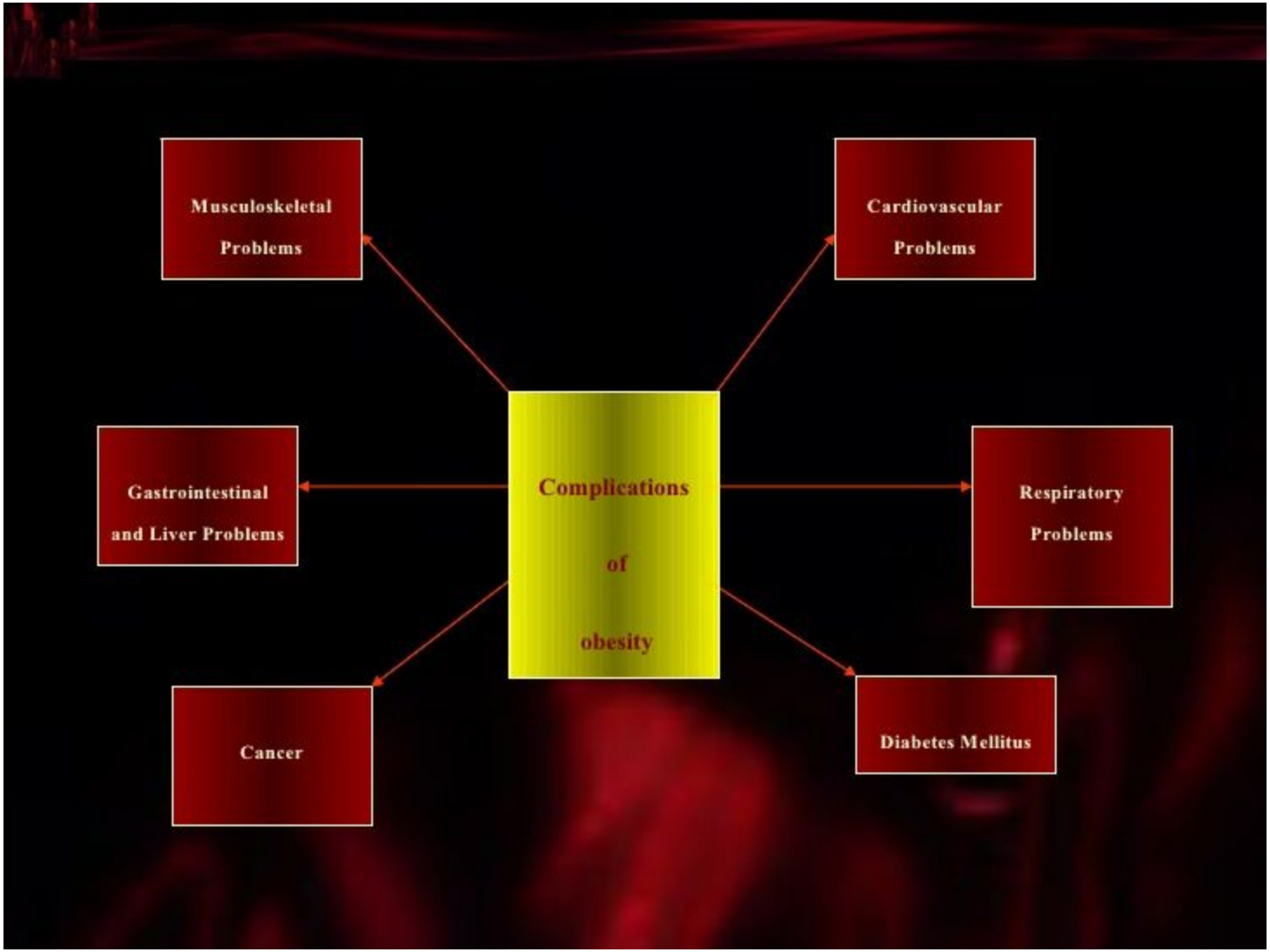


Adiponectin and Fat Mass

- Seems to be a clear relationship between adiponectin and fat mass in humans
- However, in contrast to leptin, adiponectin levels are significantly reduced among obese subjects in comparison with lean control subjects.
- Mean plasma adiponectin levels were 3.7 mg/ml in a group of obese patients whereas in non-obese subjects it was ~ 8.9 mg/ml
- In a recent longitudinal study, plasma adiponectin concentrations decreased with increasing adiposity in a group of children evaluated.
- ONLY ADIPOSE SPECIFIC PROTEIN THAT IS NEGATIVELY REGULATED IN OBESITY

Effects of Adiponectin on Vascular Homeostasis and Insulin Resistance

Adipokines	Vascular action	Insulin action and resistance
Adiponectin	↓ ICAM-1, VCAM-1, E-Selectin ↓NFκB ↓transformation of macrophages to foam cells ↓ VSMC proliferation and migration	Plasma levels inversely correlated with obesity and insulin resistance ↑ insulin sensitivity ↓ TNF-induced changes in adhesion molecule expression

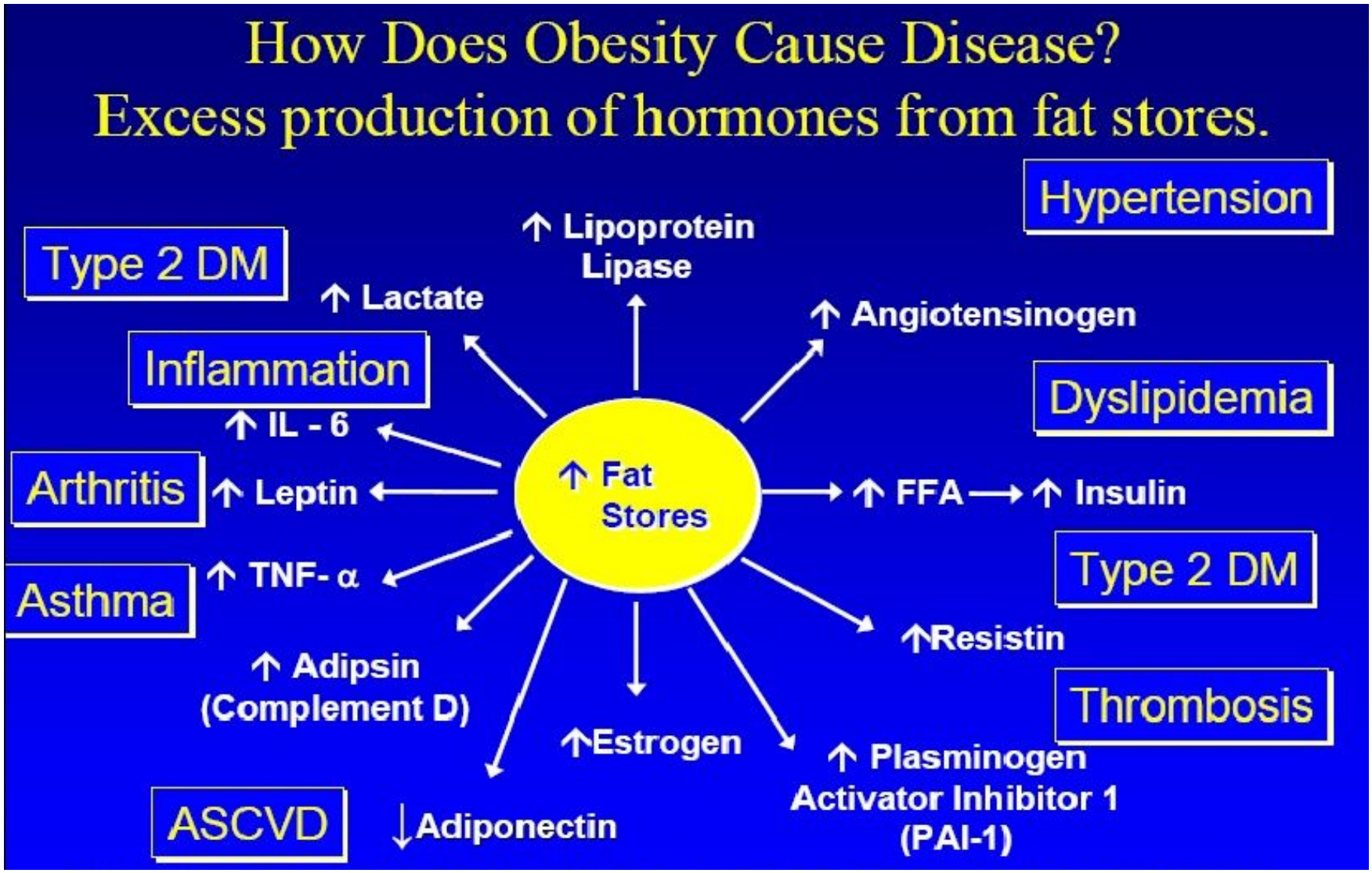

Musculoskeletal Problems
Cardiovascular Problems
Gastrointestinal and Liver Problems
Complications of obesity
Respiratory Problems
Cancer
Diabetes Mellitus

Cardiovascular Diseases Associated with Obesity

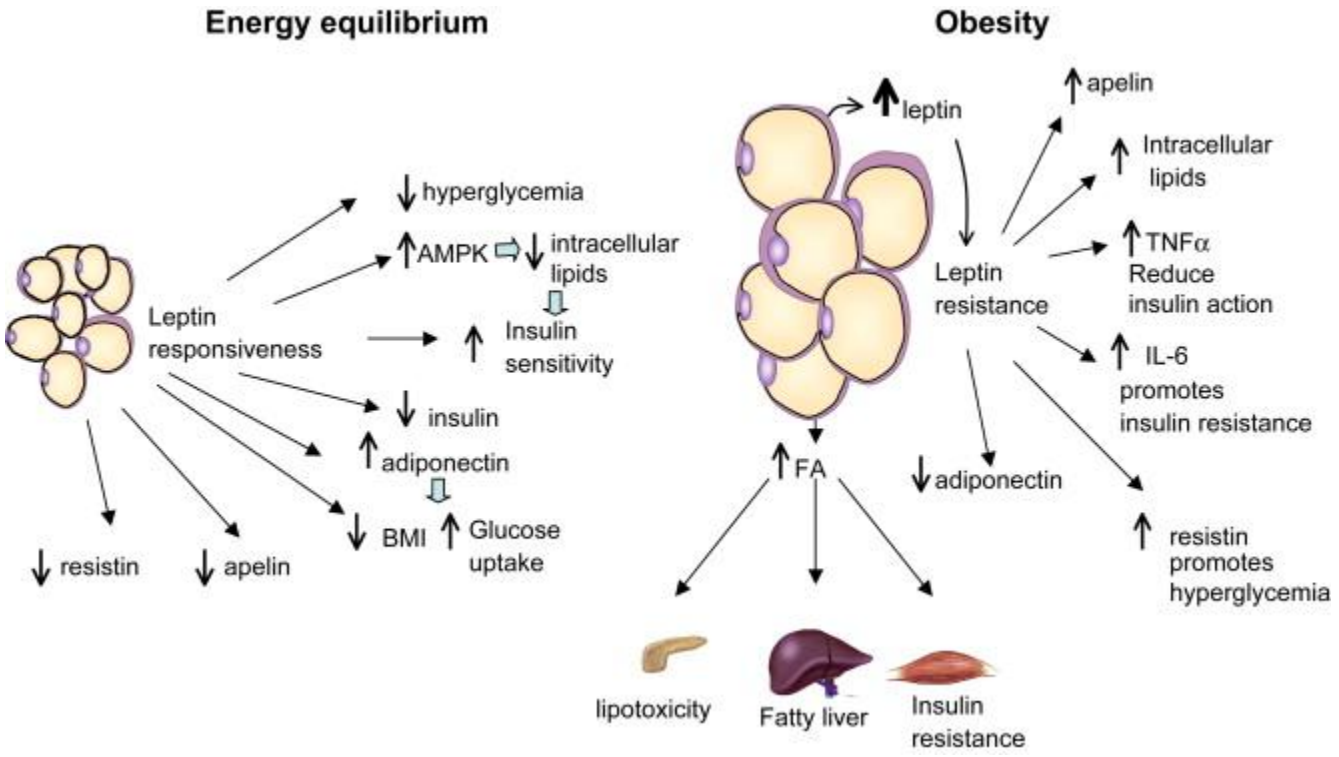
- Obesity is a significant risk factor for predicting cardiovascular disease

- Risks
  - High LDLSs
  - High Triglycerides
  - Low HDLS
  - Hypertension
  - Increased circulating blood volume
  - Abnormal vasoconstriction
  - Blunted vascular relaxation
  - Increased cardiac output

- Diabetes: 80% related to obesity
- Hypertension: prevalence is >40% in obesity
- Heart disease: 70% related to obesity
- Cancer: Obesity accounts for 15-20% of cancer-related deaths
- **Death: Obese individuals have a 50-100% increased risk of death from all causes compared to lean individuals** (most of this risk is due to cardiovascular disease)

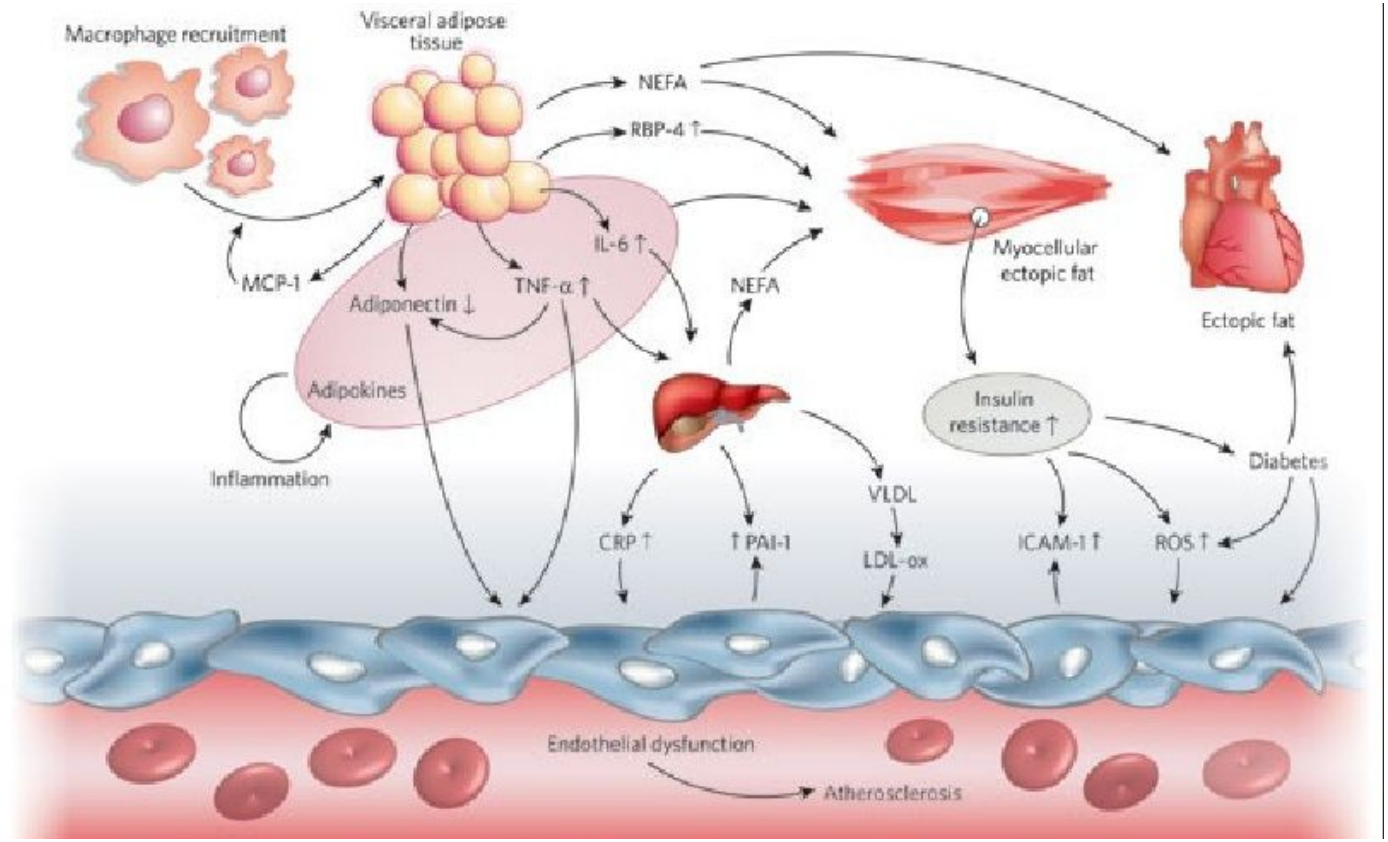

How Does Obesity Cause Disease?
Excess production of hormones from fat stores.
Hypertension
↑ Lipoprotein Lipase
Type 2 DM
↑ Lactate
↑ Angiotensinogen
Inflammation
Dyslipidemia
↑ IL - 6
Arthritis
↑ Leptin
↑ Fat Stores
↑ FFA → ↑ Insulin
Type 2 DM
Asthma
↑ TNF- α
↑Resistin
↑ Adipsin (Complement D)
Thrombosis
↑Estrogen
↑ Plasminogen Activator Inhibitor 1 (PAI-1)
ASCVD
↓Adiponectin

Adipocyte response and factors secreted from white adipose tissue during energy equilibrium and obesity



Adipocytes during energy equilibrium are leptin responsive and nonhypertrophic -therefore, nonadipose tissues are leptin and insulin sensitive. Under this condition adipocytes secrete adipokines to stimulate insulin sensitivity and fatty acids (FA) oxidation. Adipocytes during obesity are hypertrophic and nonadipose tissues are resistant to leptin and insulin action. Adipocytes secrete high amounts of FAs as well as adipokines that promote insulin resistance resulting in ectopic accumulation of lipids in pancreas, liver and skeletal muscle.

Adipokines and Cardiovascular Disease



Both visceral fat and insulin resistance contribute to cardiovascular disease in obesity

What happens to adipose tissue in obesity?

1. Adipocyte Hypertrophy & Hyperplasia

   Hypertrophy: increased size of adipocytes

   Hyperplasia: increased numbers of adipocytes

2. Spillover of fatty acids into the blood – lipotoxicity
3. Unregulated production and secretion of adipokines
4. Decreased adipose tissue blood flow…particularly postprandially
5. *Infiltration of adipose tissue by macrophages!*

The Role of Macrophage Infiltration

(1) Macrophages: a recap

- Originate from monocytes in the blood
- Traditionally thought of only as immune cells – phagocytes

What they do:

- Angiogenesis – important in the formation of new blood vessels (especially in inflammation and ischaemia)
- Clearing of necrotic tissue
- Secretion of pro-inflammatory cytokines i.e. TNF-α

GOOD VS. EVIL!

(2) Alternative vs. Classical Activation of Macrophages

Macrophages develop into specialized cell types with specific functions in response to different stimuli

Two classifications of adipose tissue macrophages:

(1) Alternatively-activated macrophages:

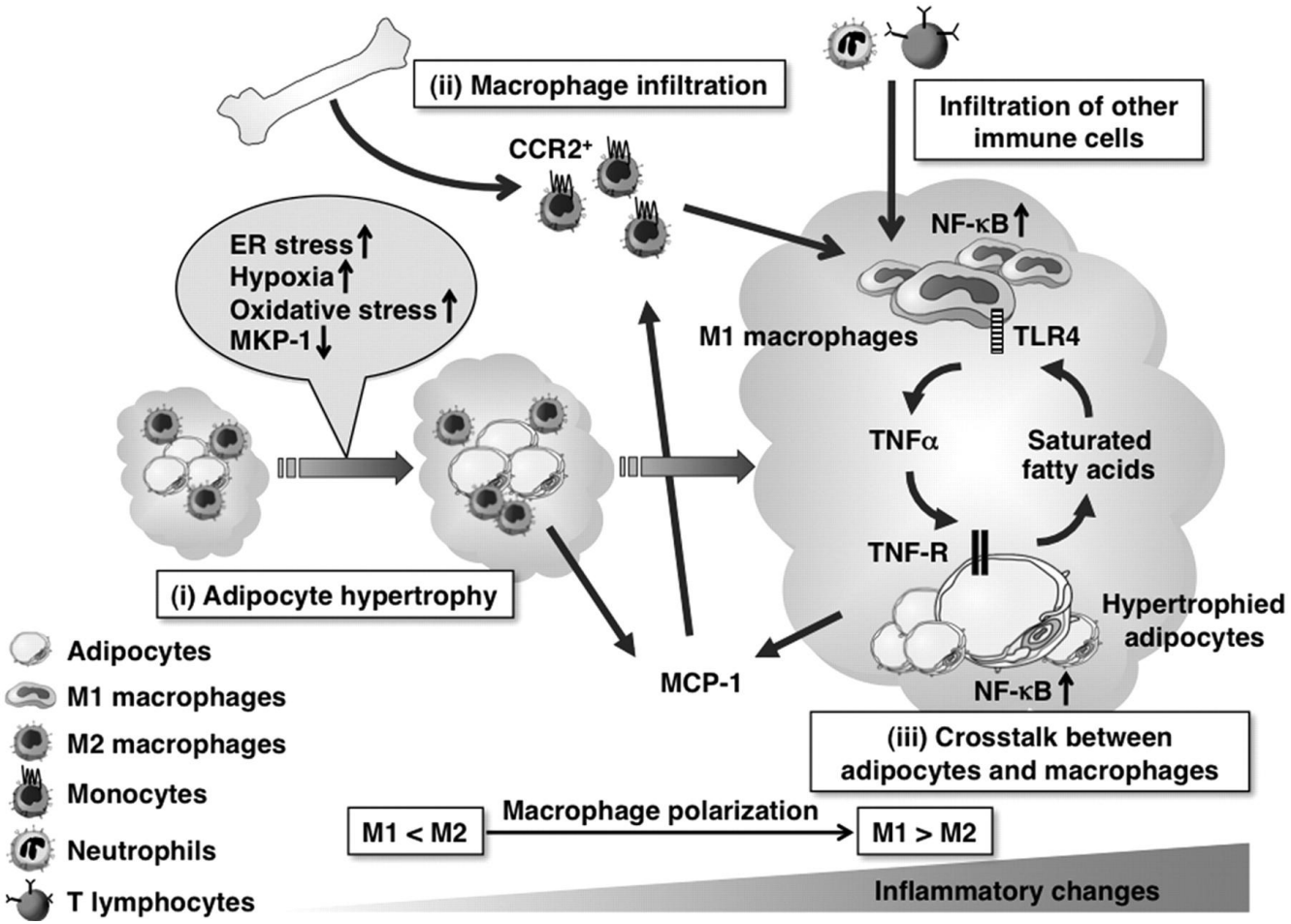
- promote angiogenesis, clear pathogens, etc.
- **GOOD**

(2) Classically-activated macrophages:

- promote inflammation, extracellular matrix destruction
- **BAD**

With obesity, see a shift from alternatively activated macrophages to classically activated macrophages

Molecular mechanism underlying adipose tissue inflammation



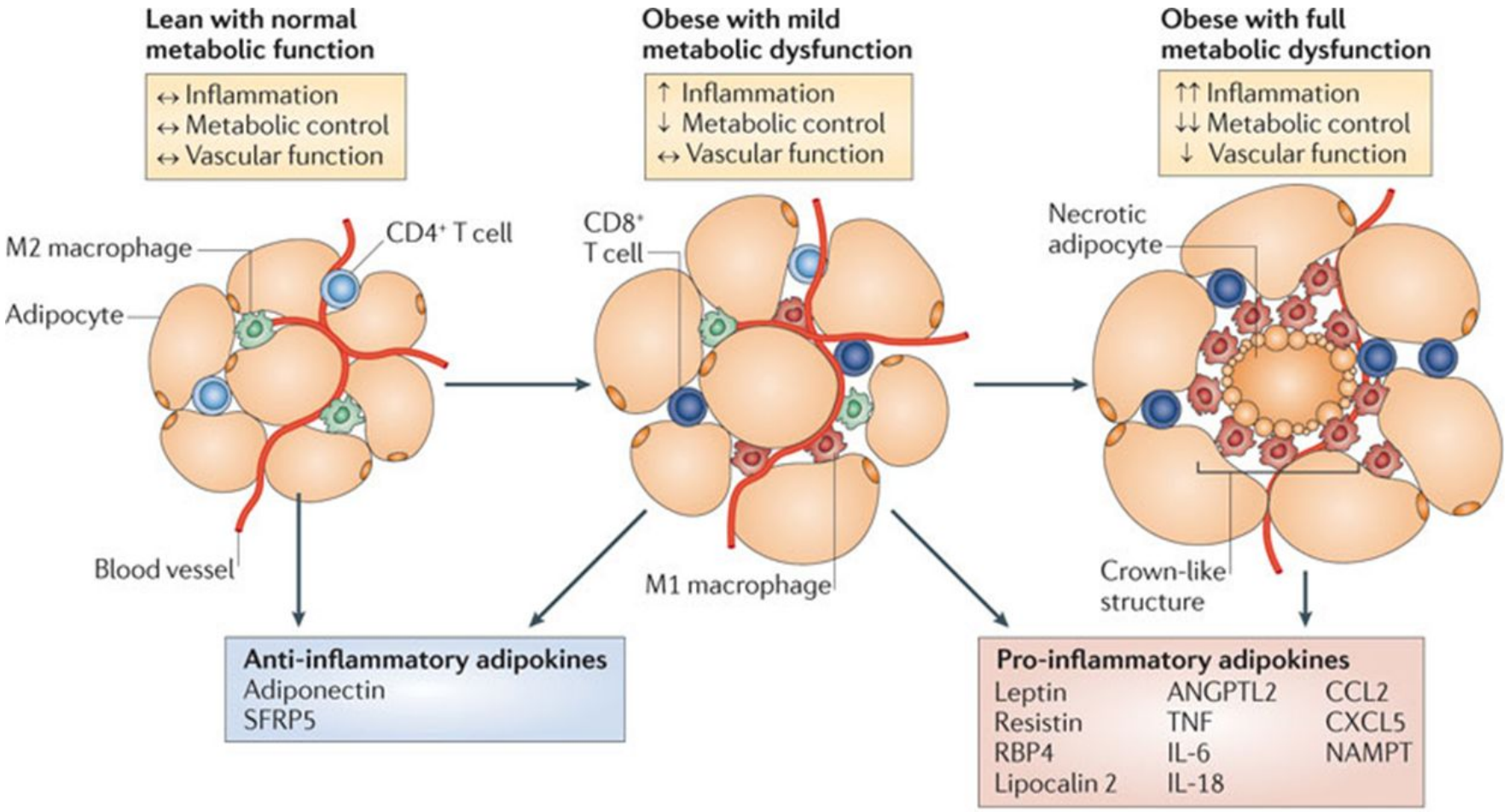
In the early stages of obesity, adipocytes become hypertrophied in response to overnutrition (i). Increased metabolic stresses such as ER stress, hypoxia, and oxidative are involved in the induction of inflammatory changes in adipocytes during the course of adipocyte hypertrophy.

In the advanced stages of obesity, there are various kinds of stromal immune cells such as neutrophils, T lymphocytes, and macrophages, which infiltrate into obese adipose tissue (ii) and enhance the inflammatory changes through the crosstalk with parenchymal adipocytes (iii). For example, the macrophage-derived TNF-α induces the release of saturated fatty acids from adipocytes via lipolysis, which in turn, induces inflammatory changes in macrophages via TLR4. Such a paracrine loop between adipocytes and macrophages constitutes a vicious cycle, thereby accelerating further adipose tissue inflammation.

Recent evidence has also pointed to the heterogeneity of adipose tissue macrophages; i.e., M1 or "classically activated" (proinflammatory) macrophages and M2 or "alternatively activated" (anti-inflammatory) macrophages. Macrophages exhibit a phenotypic change from M2 to M1 polarization in obesity, thereby accelerating adipose tissue inflammation.

Suganami T , Ogawa Y J Leukoc Biol 2010;88:33-39

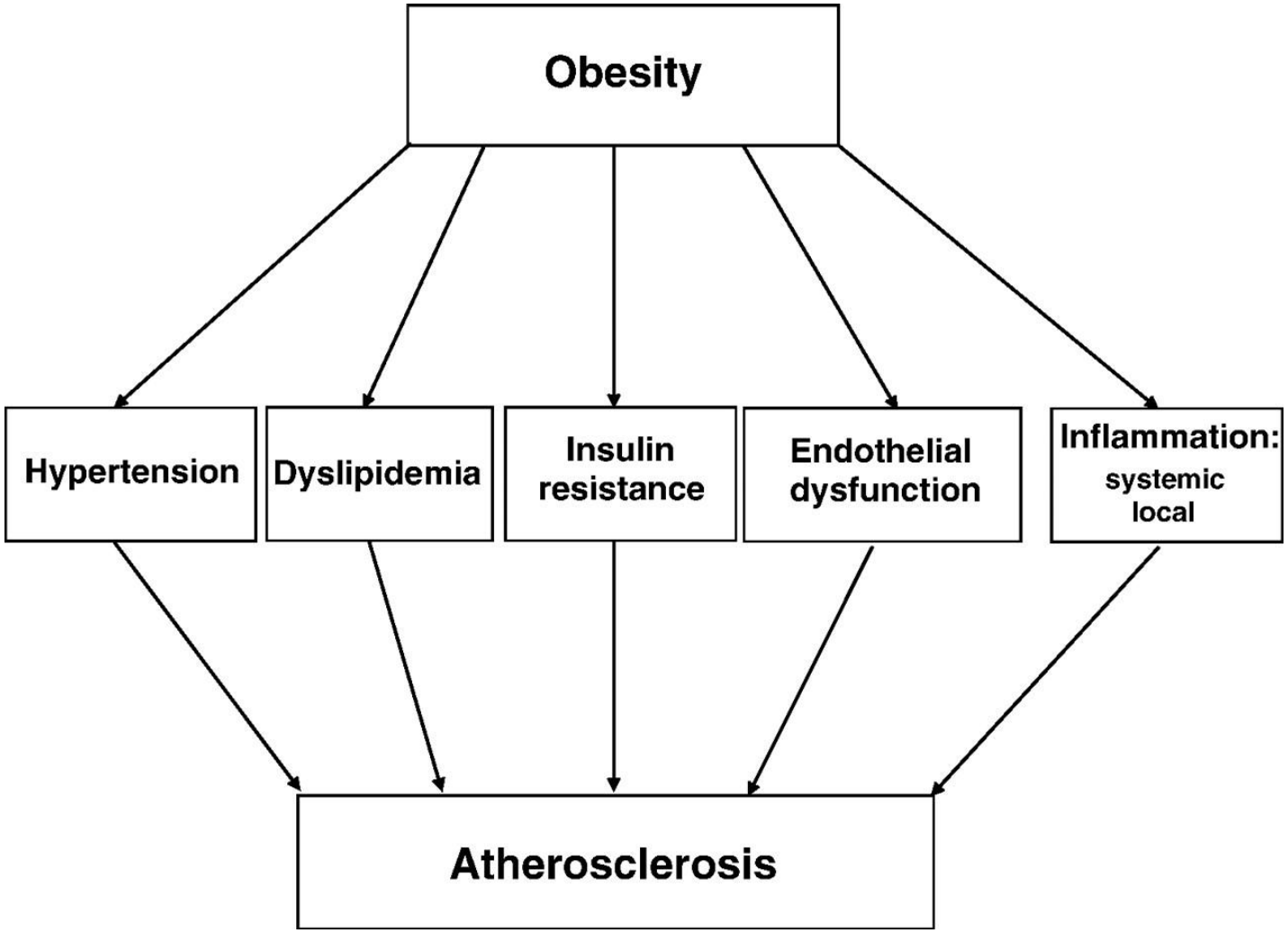
Phenotypic Modulation of Adipose Tissue



Progressive weight gain leads to adipocyte enlargement and a proinflammatory state with increased macrophage activation, secretion of chemokines and cytokines, and endothelial damage.

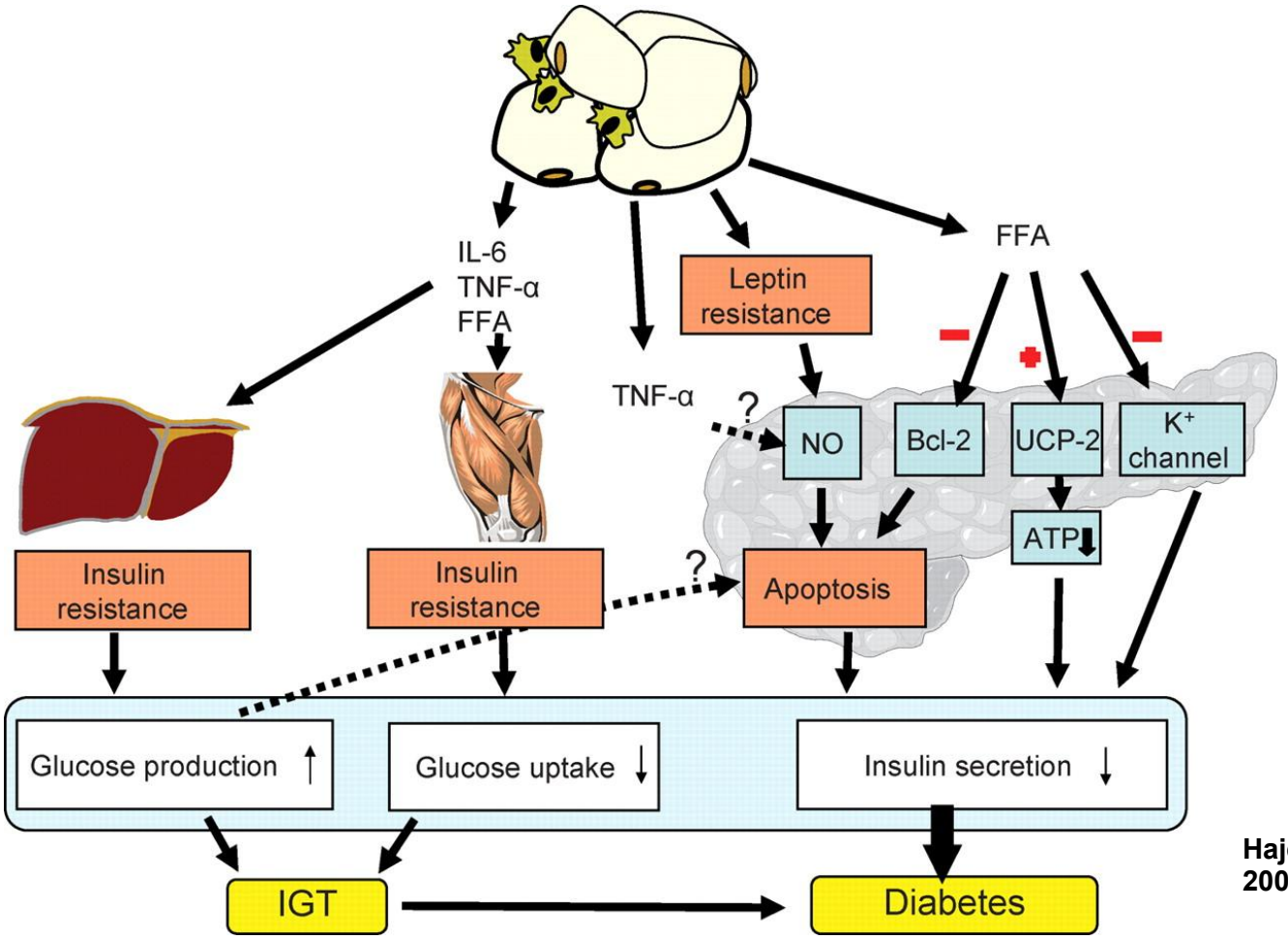
Ouchi et al., 2011

Relation between obesity and the development of atherosclerosis.



Thalmann S , Meier C A Cardiovasc Res 2007;75:690-701

Adipocyte dysfunction leads to type 2 diabetes: chronically elevated free fatty acid (FFA) levels inhibit insulin secretion.



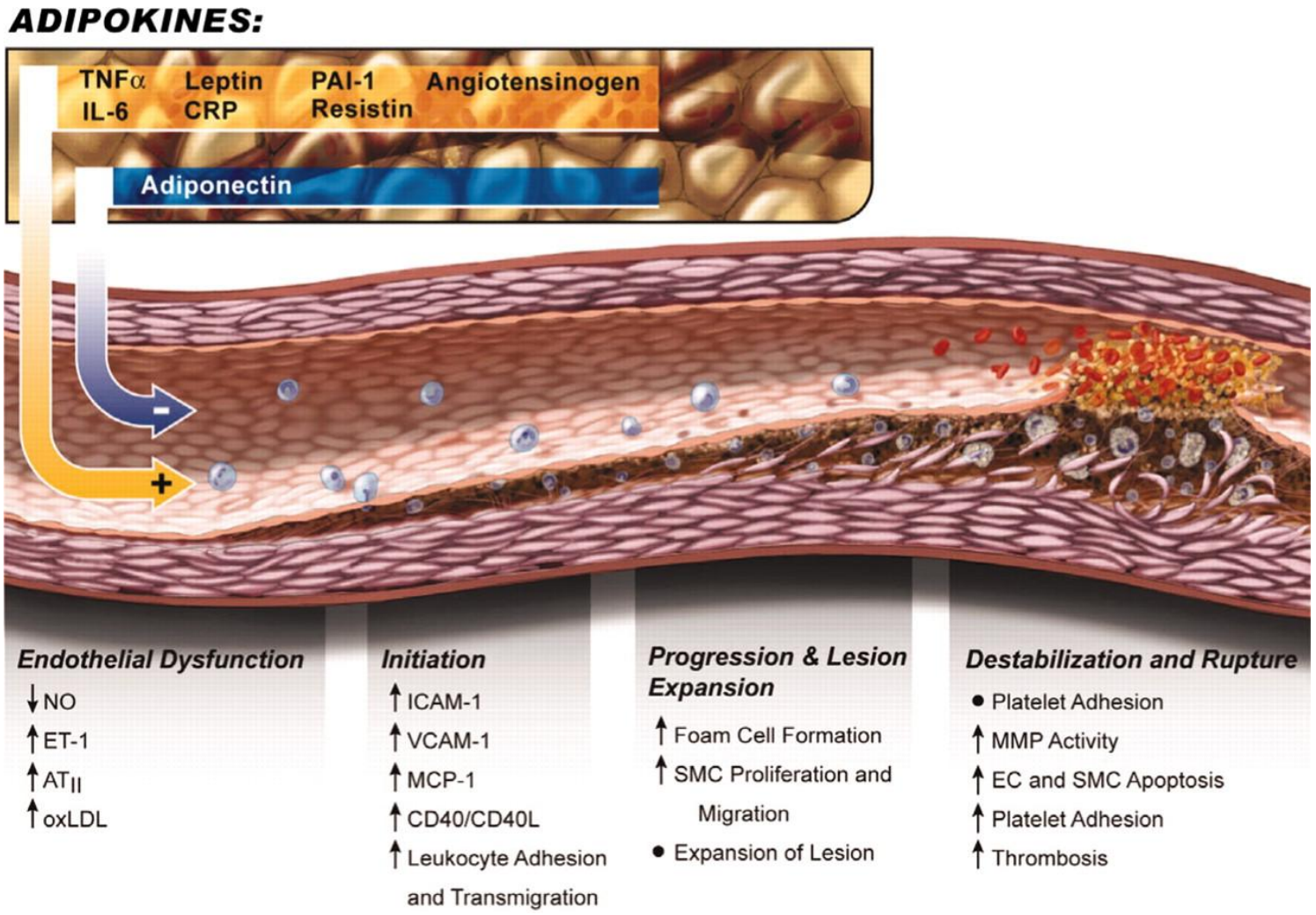
Hajer G R et al. Eur Heart J 2008;29:2959-2971

FFA can open β-cell potassium channels to diminish insulin secretion, enhance expression of uncoupling protein 2 (UCP-2) and diminish ATP production necessary for insulin secretion. FFAs also induce β-cell apoptosis via an endoplasmic stress response and by inhibiting expression of the anti-apoptotic factor Bcl-2.

Leptin has been shown to have anti-apoptotic effects in β-cells, which may be diminished in the (obese) leptin-resistant state. Anti-apoptotic effects of leptin include inhibition of NO production via reduction of triglyceride content.

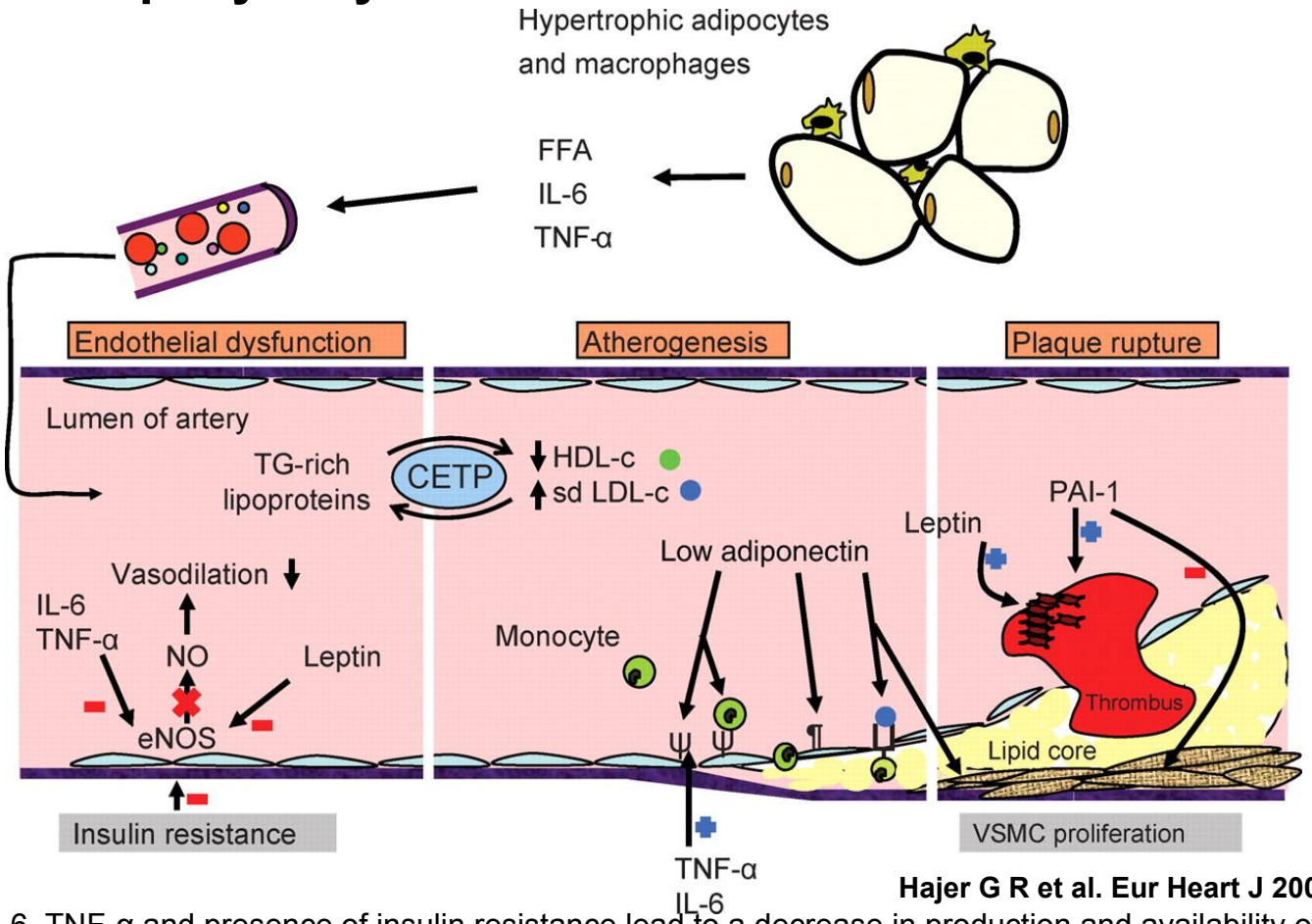
NO has been proposed to induce apoptosis via depletion of calcium stores in the ER leading to the ER stress response. By inhibiting insulin signalling in the β-cell and by induction of NO synthesis, TNF-α may reduce insulin secretion in vitro.

Anti- and proinflammatory adipokines



Lau D C W et al. Am J Physiol Heart Circ Physiol 2005;288:H2031-H2041

Adipocyte dysfunction leads to atherosclerosis



Hajer G R et al. Eur Heart J 2008;29:2959-2971

Elevated levels of IL-6, TNF-α and presence of insulin resistance lead to a decrease in production and availability of endothelial nitric oxide synthase resulting in endothelial dysfunction.

Increased adipocyte-derived cholesteryl ester transfer protein (CETP) plasma concentrations lead to decreased high density lipoprotein cholesterol and increased in small dense low density lipoprotein cholesterol particles. Adiponectin inhibits the development of atherosclerosis by inhibiting the expression of adhesion molecules intracellular adhesion molecule-1, vascular cell adhesion molecule-1 (induced by IL-6 and TNF-α) on endothelial cells by activating 5'AMP-activated protein kinase (AMPK) (in vitro), by inhibiting NF-κB and by the inhibition of scavenger receptor class A-1. This leads to reduction of cholesterol uptake in macrophages and to transformation of macrophages into foam cells.

Adiponectin reduces VSMCs, migration and apoptosis. Increased levels of plasminogen activator inhibitor-1 inhibits plasminogen-induced migration of VSMCs that lead to plaques prone to rupture with thin fibrous caps, necrotic cores and rich in macrophages. Leptin is capable of inducing ADP-dependent platelet activity and aggregation in healthy subjects.

Effects of Thiazolidinediones Mediated via Adipose Tissue