Adipocytes as an endocrine cell

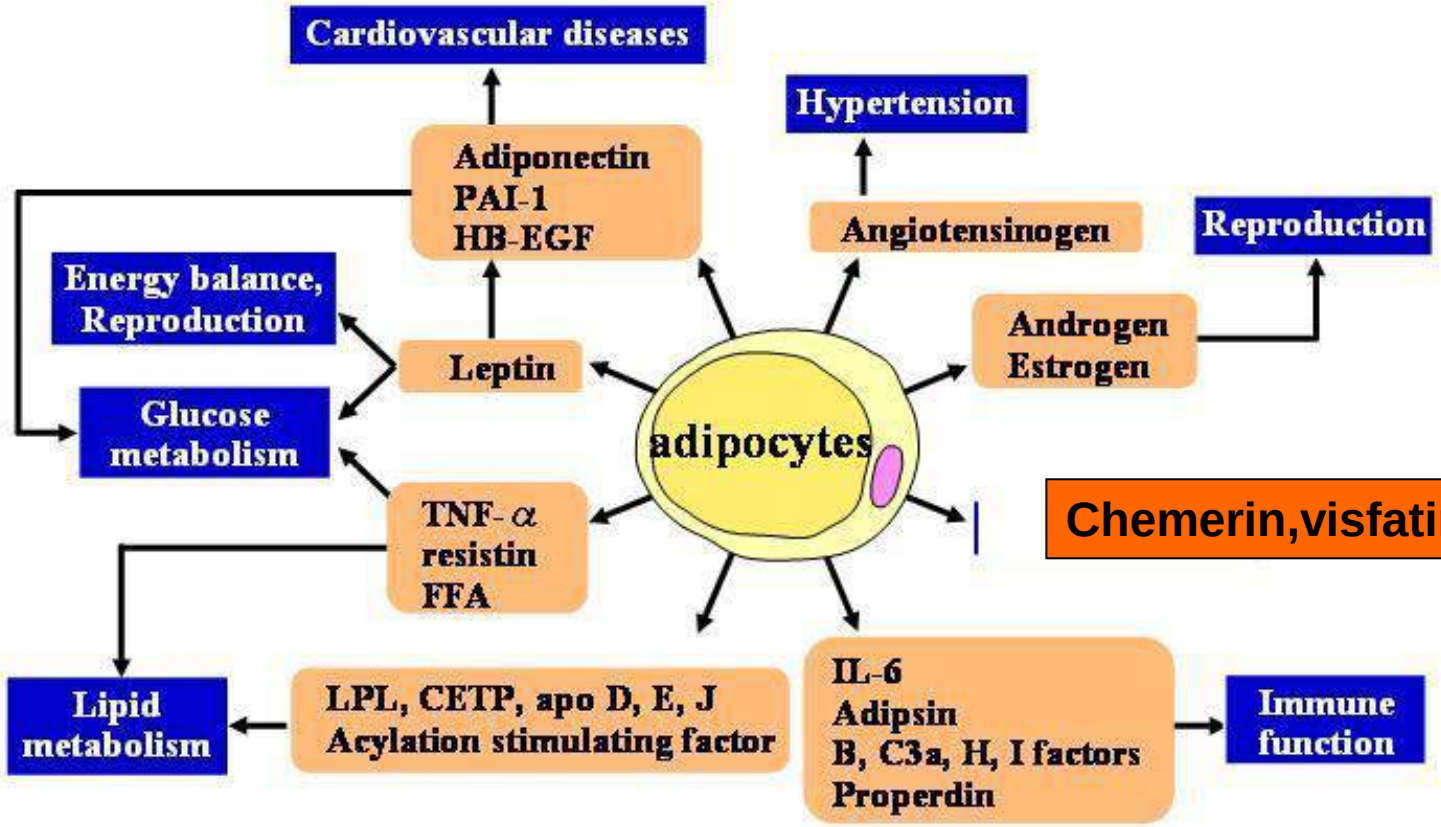


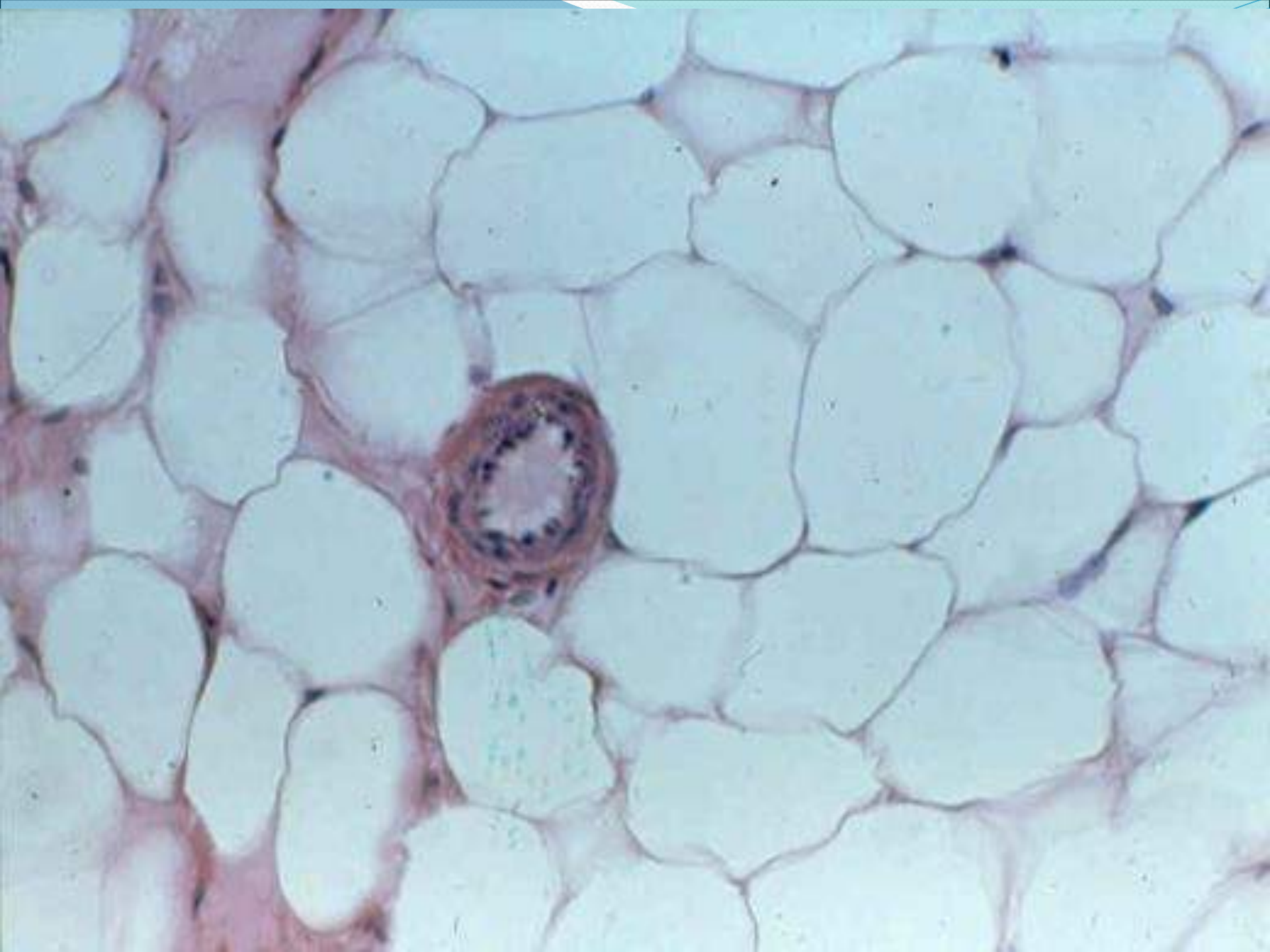
Fig. 1. Adipocytes as an endocrine cell

- Studies on white adipose tissue have led to the recognition that it is an important endocrine organ, communicating with the brain and peripheral tissues through the secretion of leptin and other adipokines

- respond to multiple body signals by secreting factors (including leptin, other cytokines, adiponectin, complement components, plasminogen activator inhibitor-1, resistin, and proteins of the renin-angiotensin system) with important endocrine functions
- Metabolism of sex steroids and glucocorticoids also takes place in adipose tissue

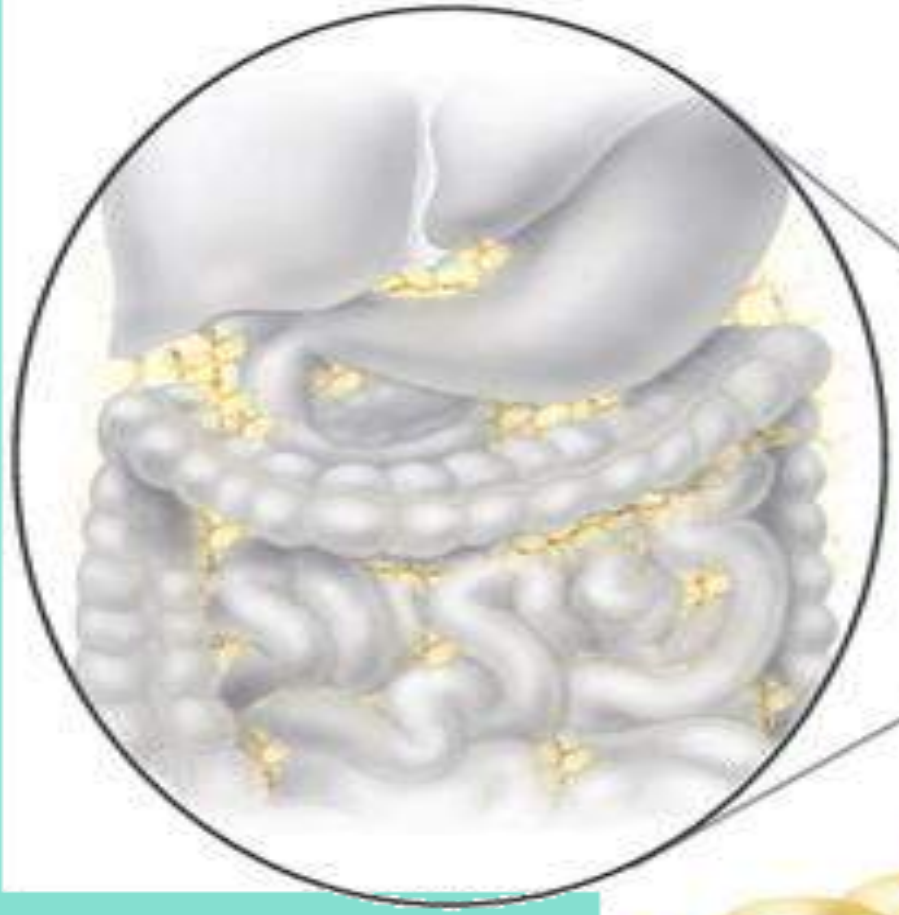
- Ectopic fat deposition
- Normal fat deposition
- Hormones of adipose tissue
- Their production their normal concentration their trigger and finally their action in healthy and diseases apart from their biochemical structure

- The contents of adipose tissue (including adipocytes, connective tissue matrix, nerve tissue, immune cells, stromovascular cells, and immune cells



- Excessive visceral fat (i.e., mesenteric and omental fat) is associated with insulin resistance and diabetes
- waist circumference, which correlates with visceral fat mass has been recommended as a clinical marker to identify patients at increased risk for metabolic diseases

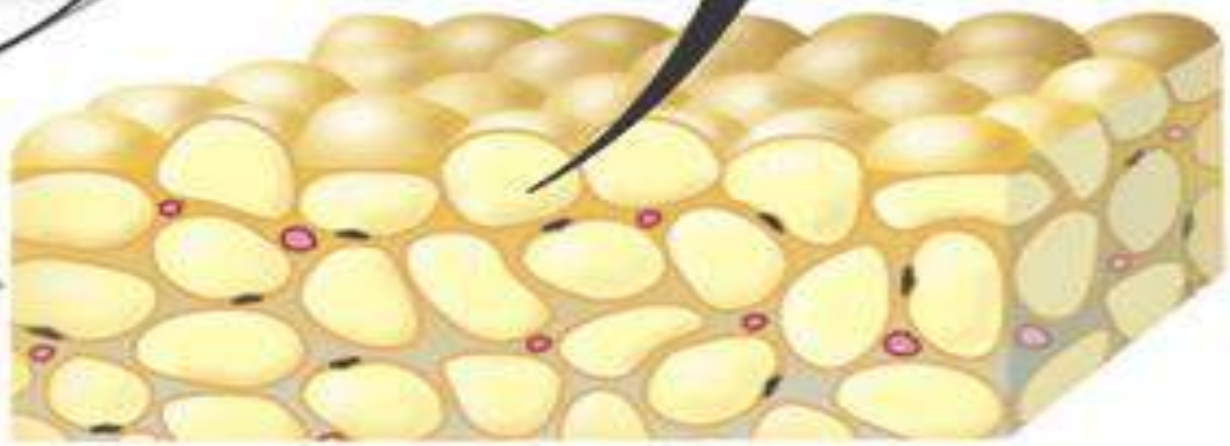
- Visceral fat could cause metabolic abnormalities by secreting inflammatory adipokines, such as interleukin (IL)-6, tumor necrosis factor- (TNF-), macrophage chemoattractant protein-1 (MCP-1), and resistin, which induce insulin resistance and diabetes



Selected adipokines

Leptin
Adiponectin
Resistin
TNF-α
IL-6
Visfatin

Preadipocytes



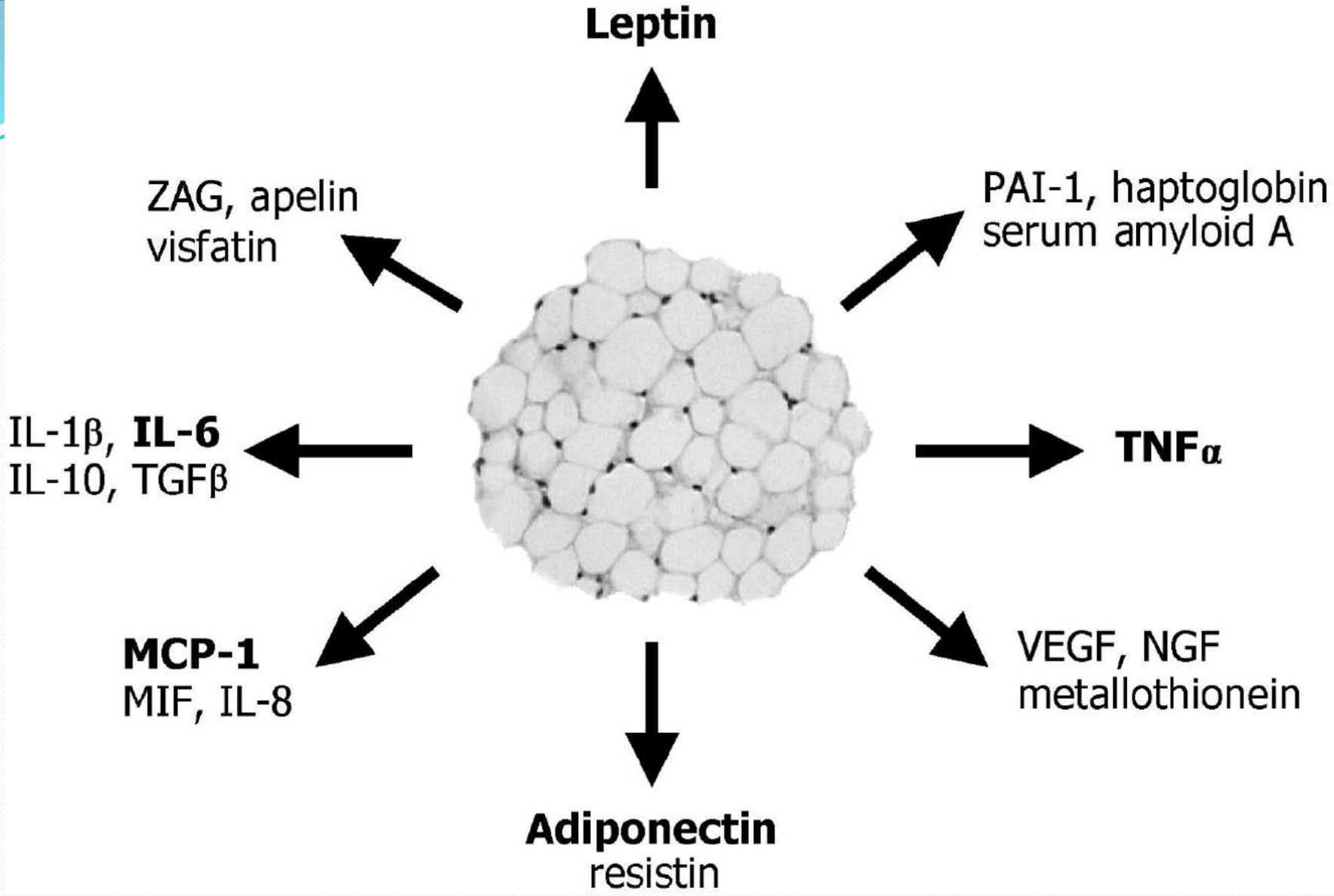
Mature adipocytes
adipose tissue

- Strict physiological controls exist for the use and storage of adipose 'tissue so that thermoregulatory and metabolic demands for energy can be sustained. Such controls are affected by hormonal and neural mediators, often interacting both at peripheral and central sites

- Women have a higher percentage of body fat than men, and there is a gender-specific difference in fat distribution: Females tend to accumulate fat around the hips, buttocks, and thighs while men have a larger intra-abdominal (visceral) fat mass.

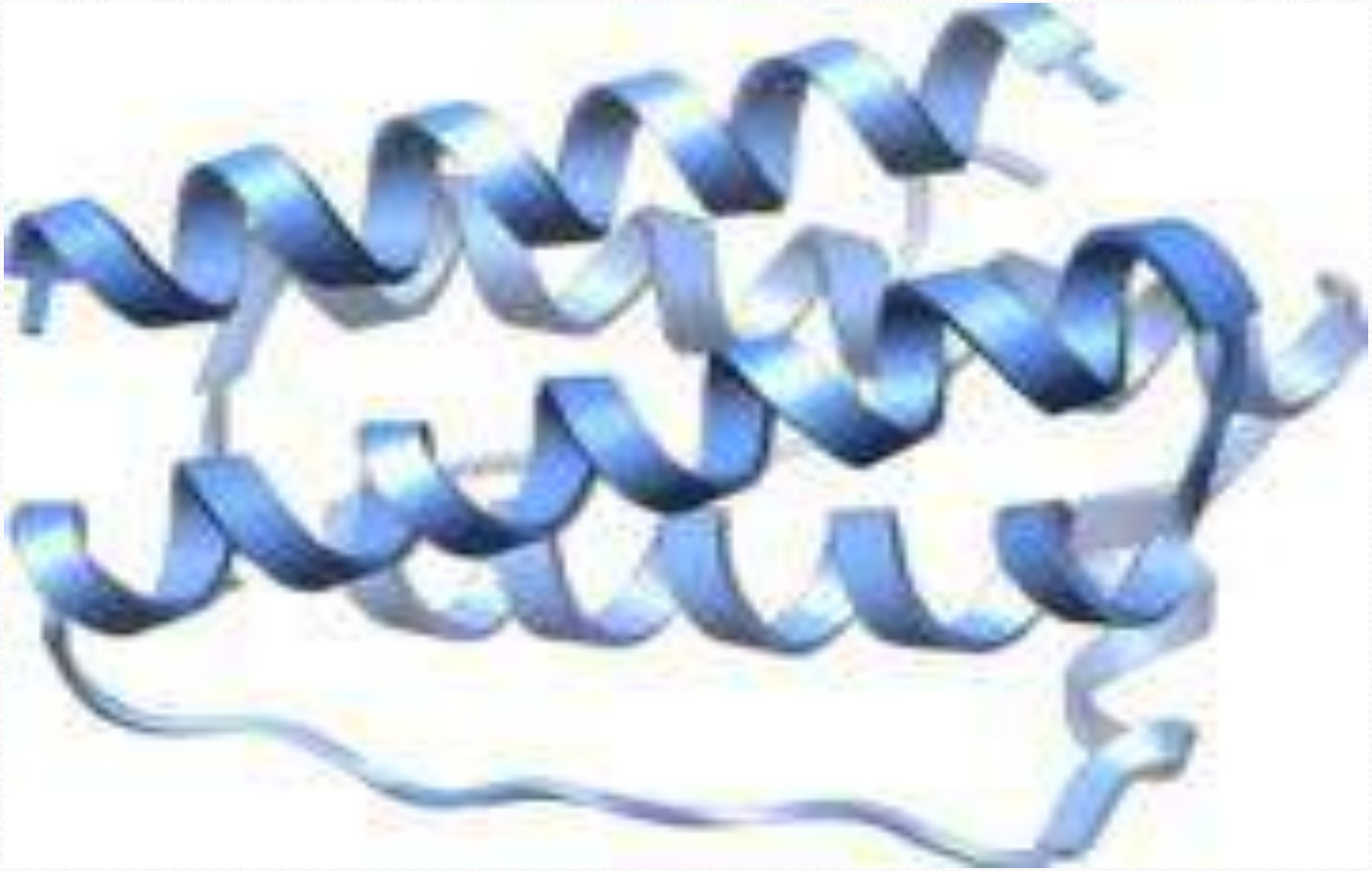
Products of adipose tissue

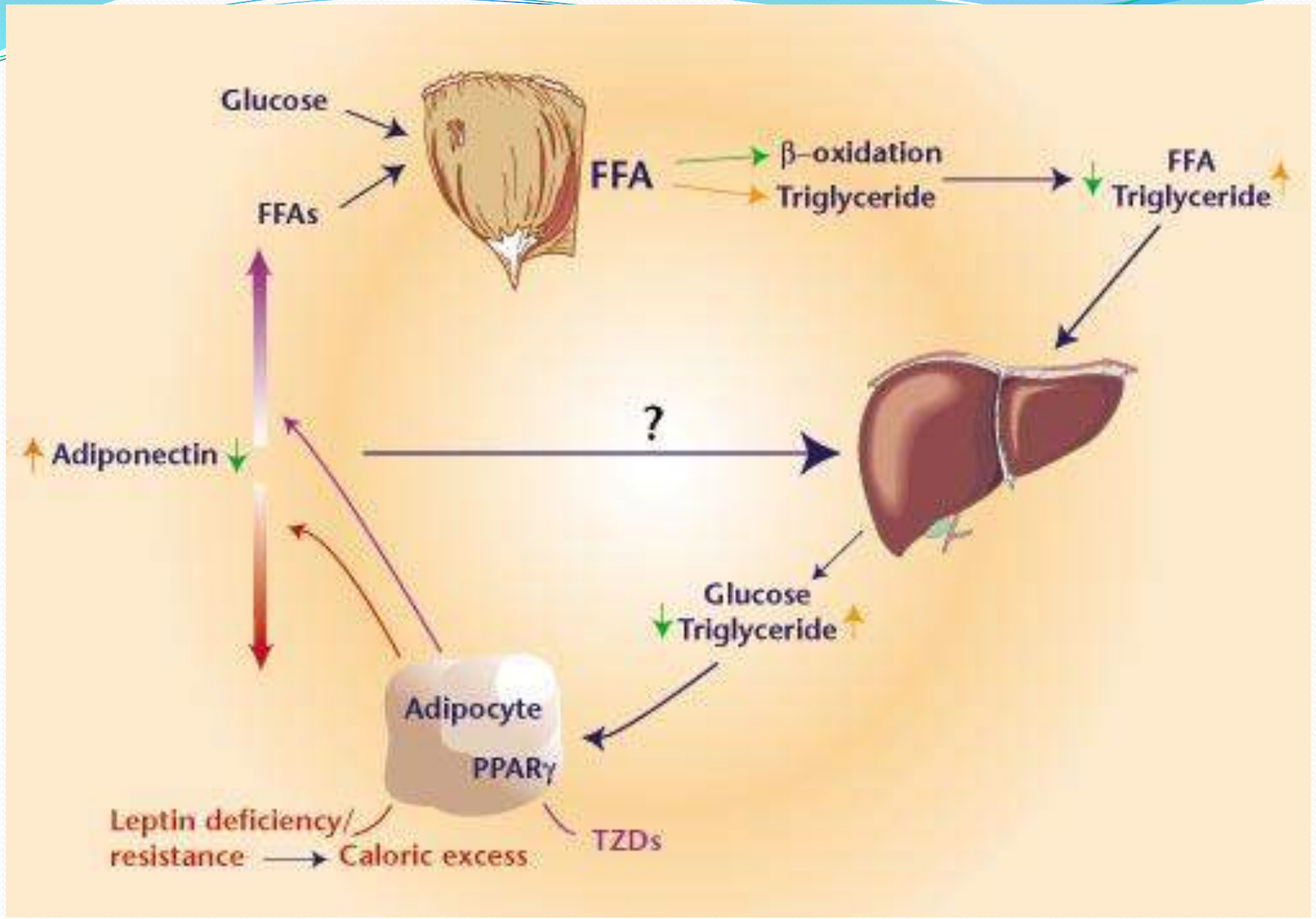
- proteins such as adiponectin, leptin, resistin are referred to as adipose derived hormones.
- and the **adipokines** or **adipocytokines** are a group of cytokines (cell-to-cell signalling proteins) secreted by adipose tissue .

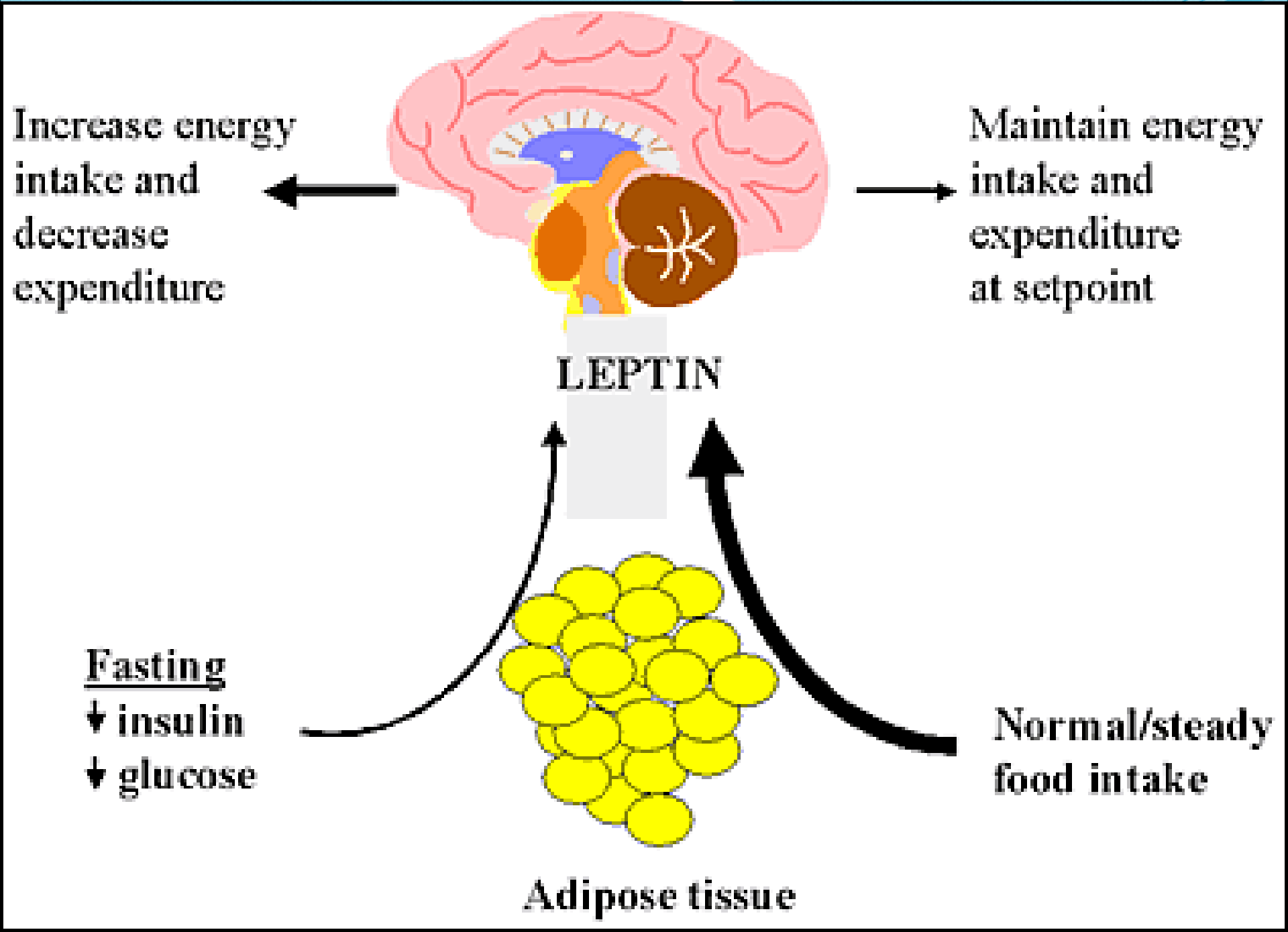


- Major adipokines secreted from white adipose tissue. The figure shows some of the key adipokines, particularly those linked to inflammation. TGF-*ß*, transforming growth factor-*ß*; ZAG, zinc- 2-glycoprotein

leptin

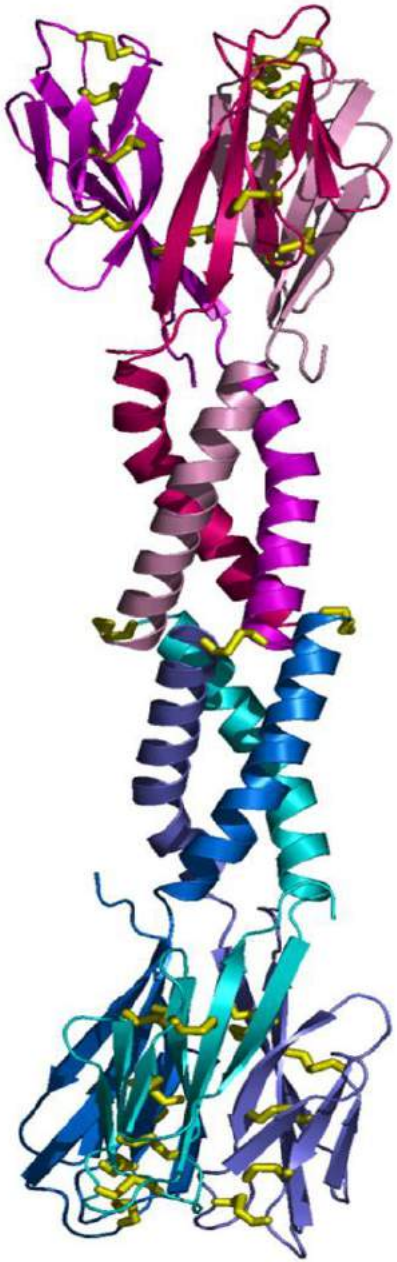



Glucose
FFAs
FFA
β–oxidation
Triglyceride
FFA
Triglyceride
Adiponectin
?
Glucose
Triglyceride
Adipocyte
PPARγ
Leptin deficiency/
resistance
Caloric excess
TZDs

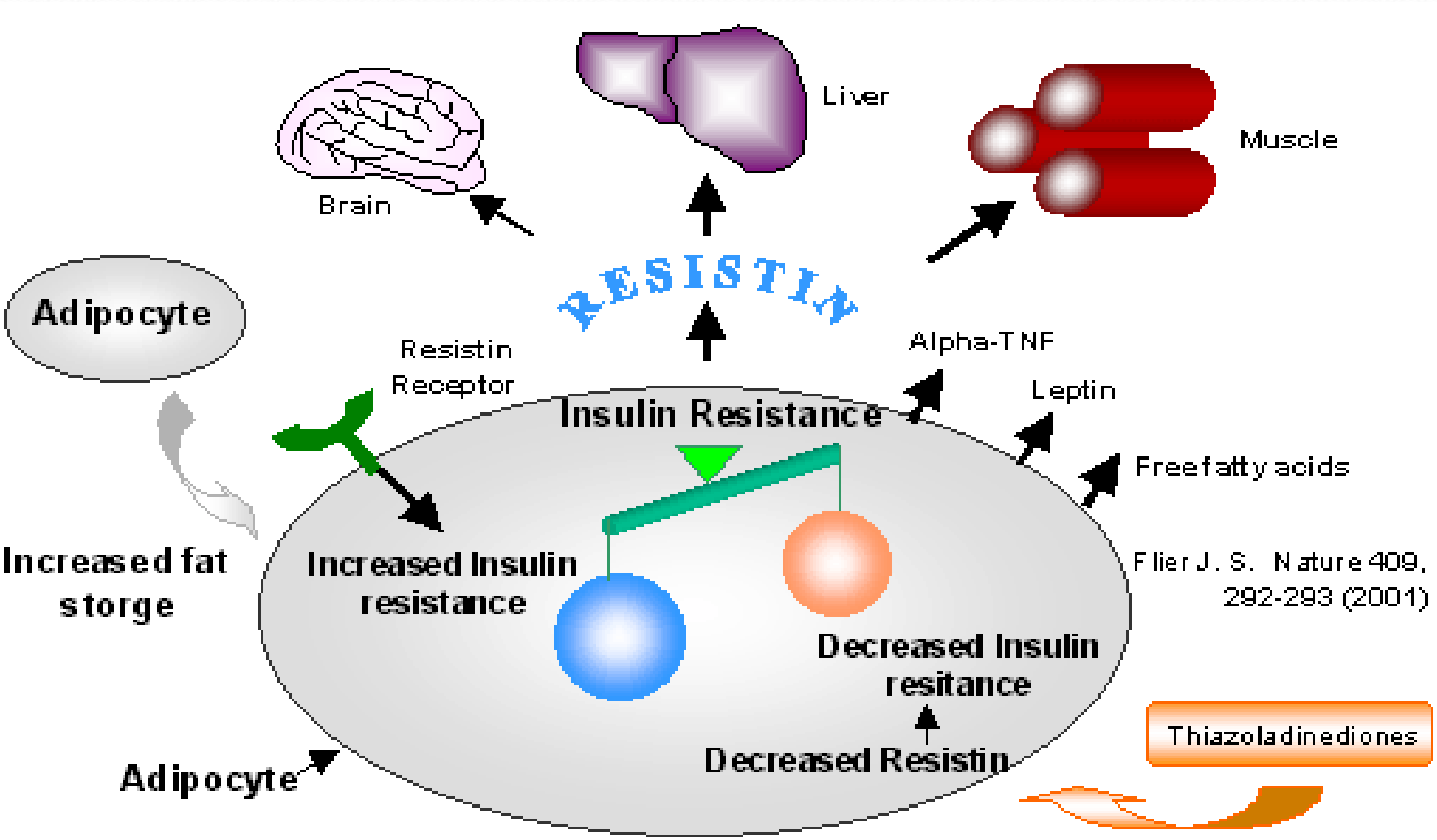

Increase energy intake and decrease expenditure
Maintain energy intake and expenditure at setpoint
LEPTIN
Fasting
insulin
glucose
Normal/steady food intake
Adipose tissue

- leptin's primary role is to signal energy deficiency to the brain, leading to adaptive responses including hyperphagia, reduced thermogenesis, and suppression of thyroid, reproductive, and immune function

- Leptin is a signal of nutritional sufficiency and decreases in response to starvation, caloric restriction, or weight loss
- Leptin levels are elevated in common forms of obesity, indicating a state of leptin resistance
- Other important endocrine effects of leptin include immune function regulation, hematopoiesis, angiogenesis, and bone development.

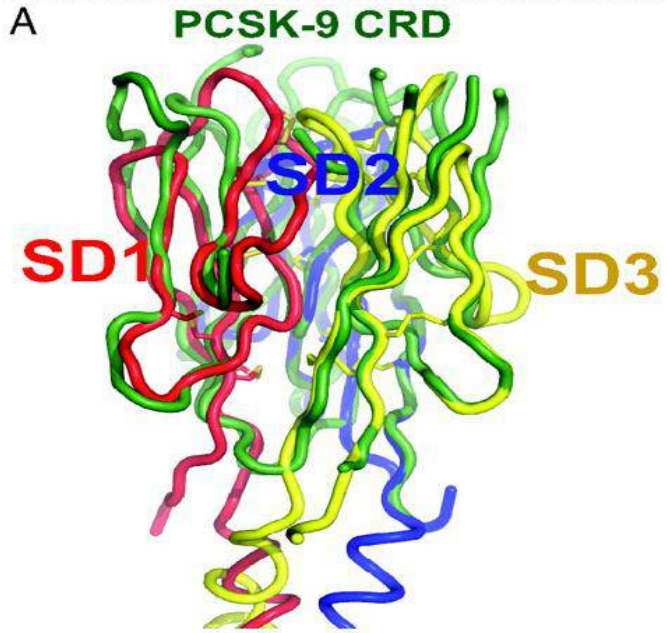


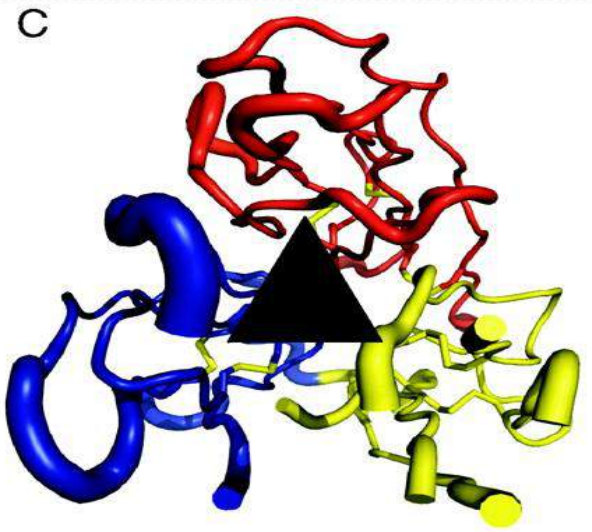
Disulfide-dependent multimeric assembly of resistin family hormones

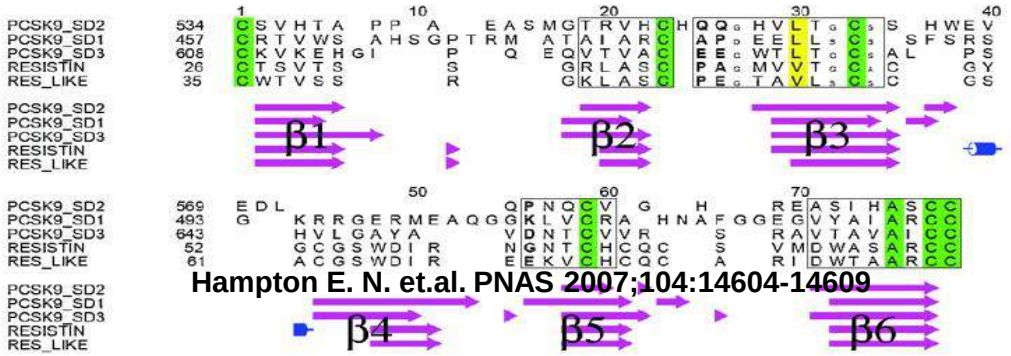


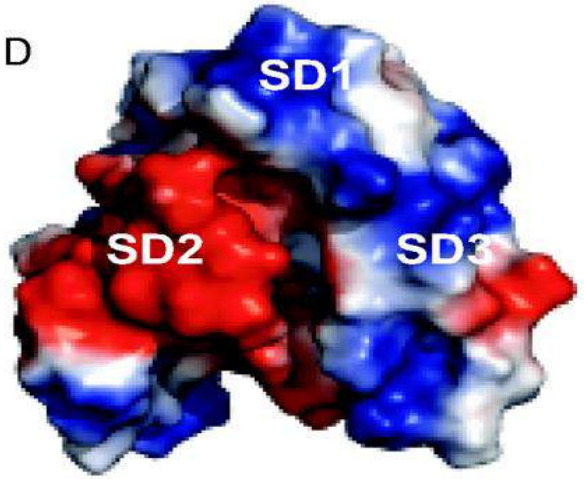
Resistin to be identified as an adipocyte-derived mediator of insulin resistance

Structural alignments of the CRD heterotrimer with the resistin homotrimer

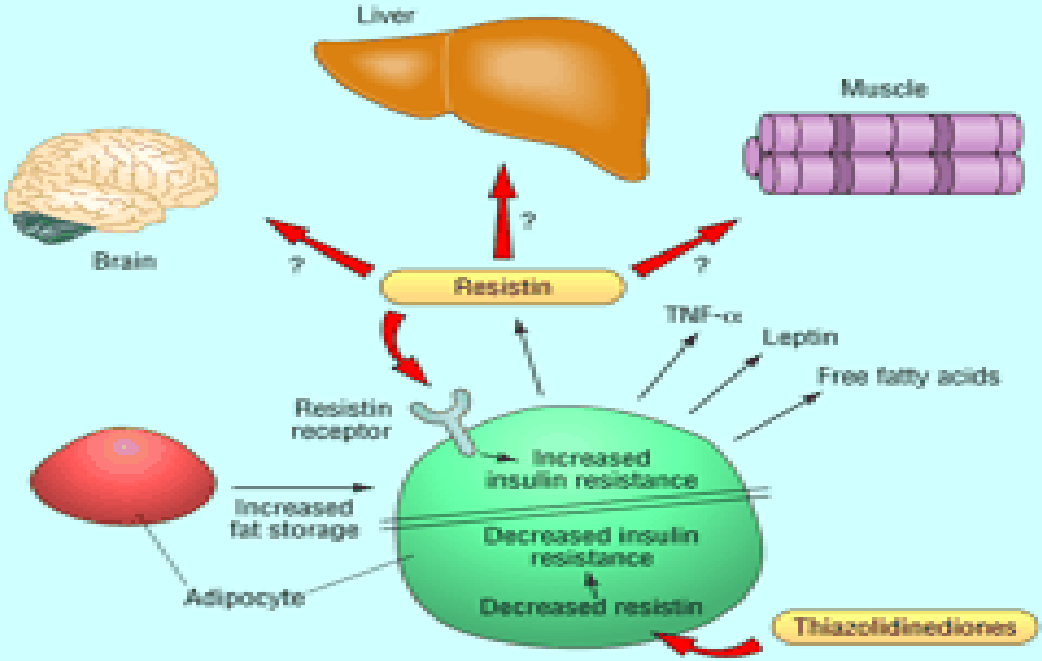








Hampton E. N. et.al. PNAS 2007;104:14604-14609



- The polypeptides adipsin and resistin are positively correlated with adiposity, insulin resistance, dyslipidemia, and cardiovascular disease.

adiponectin

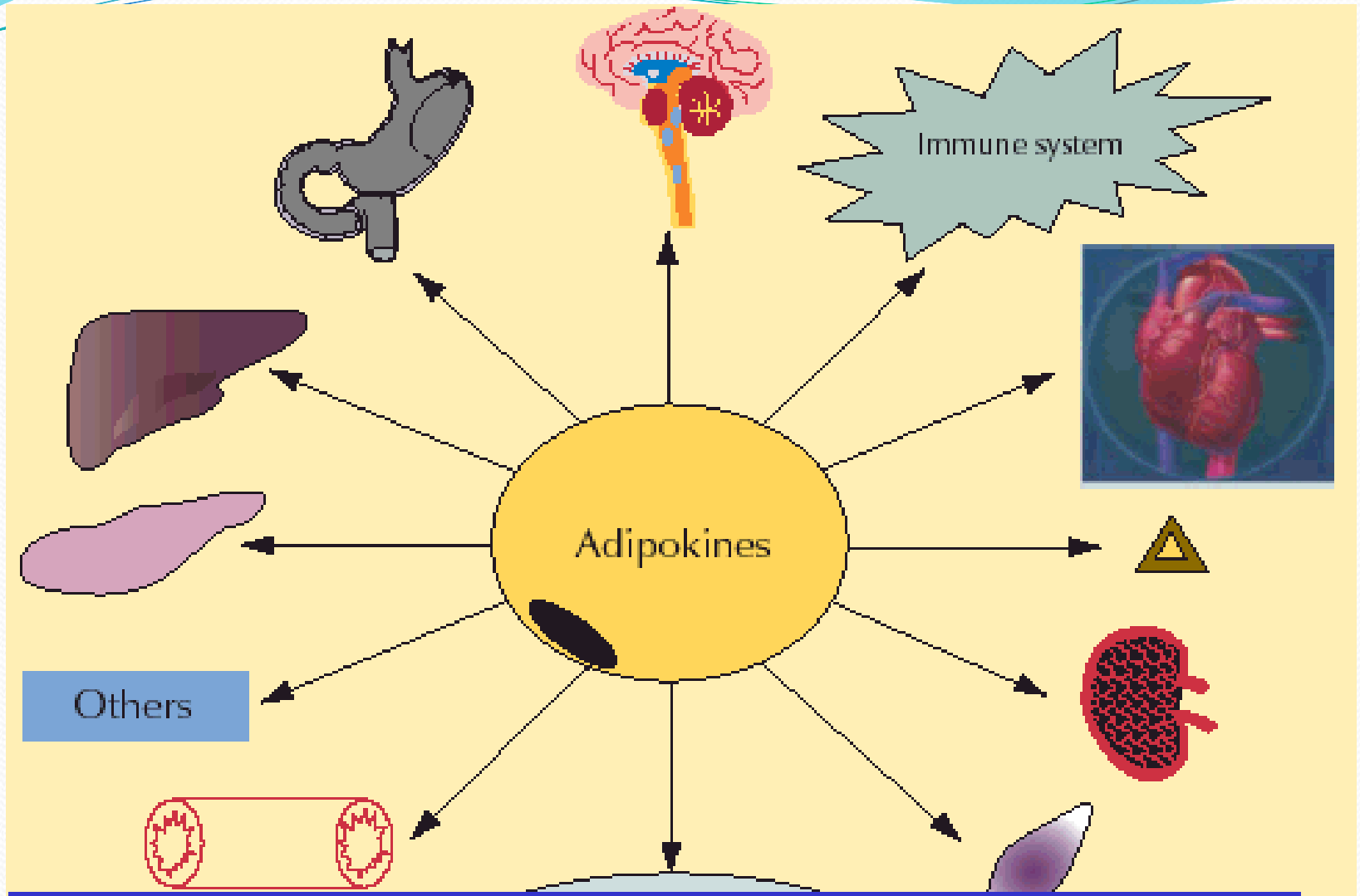
- Many of these so-called regulate energy balance, glucose, and lipids and may contribute to diseases associated with obesity
- Adiponectin appears to actually improve hepatic insulin sensitivity, reduce hepatic glucose output, and increase glucose use in the muscle

Biological activity of fat-derived hormone Adiponectin

- Beneficial effects on lipid metabolism
- Sensitizing insulin to inhibit gluconeogenesis
- Reverses insulin resistance associated with both lipoatrophy and obesity
- Directly effects on hepatic tissue and inhibit glucose production
- Hepatoprotective effects on alcoholic and nonalcoholic liver diseases
- Anti-atherogenic properties
- Protection of experimental models of vascular injury
- Anti-inflammatory effects

Pathophysiology of fat-derived hormone Adiponectin

- Reduction in adiponectin expression is associated with insulin resistance in some animal models.
- ADI sensitizing insulin to reduce plasma Glucose.
- In humans, adiponectin levels are inversely related to the degree of adiposity and positively associated with insulin sensitivity both in healthy subjects and in diabetic patients.
- Plasma adiponectin levels are decreased in some insulin-resistant states, such as obesity and type 2 diabetes mellitus, and also in patients with coronary artery disease.
- Increase of plasma adiponectin levels are associated in chronic renal failure, type 1 diabetes and anorexia nervosa.
- Concentrations of plasma adiponectin are correlate negatively with glucose, insulin, triglyceride levels and body mass index, and positively with high-density lipoprotein-cholesterol levels and insulin-stimulated glucose disposal.
- Weight loss and therapy with thiazolidinediones increased endogenous adiponectin production in humans.



A cytokine (tumor necrosis factor-α, interleukin-6) produced by adipose tissue and acting locally in an autocrine-paracrine fashion or systemically as a hormone.

- The **adipokines** or **adipocytokines** are a group of cytokines (cell-to-cell signalling proteins) secreted by adipose tissue.

Members include:

- chemerin
- interleukin-6 (IL-6)
- plasminogen activator inhibitor-1 (PAI-1)
- retinol binding protein 4 (RBP_4)
- tumor necrosis factor-alpha (TNFα)
- visfatin

- **Chemerin** (also known as **tazarotene-induced gene 2 TIG2**, **retinoic acid receptor responder 2** RARRES2) is a chemoattractant protein that acts as a ligand for the G-protein coupled receptor CMKLR1 (also known as ChemR23).
- Chemerin is a 14kDa protein secreted in an inactive form as prochemerin and is activated through by inflammatory and coagulation serine proteases.
- Chemerin was found to stimulate chemotaxis of dendritic cells and macrophages to the site of inflammation.
- In humans, chemerin mRNA is highly expressed in white adipose tissue, liver and lung while its receptor, CMKLR1 is predominantly expressed in immune cells as well as adipose tissue.
- Because of its role in adipocyte differentiation and glucose uptake, chemerin is classified as an adipokine.

visfatin

- Nampt/PBEF was recently re-identified as a "new visceral fat-derived hormone" named visfatin
- It is reported that visfatin is enriched in the visceral fat of both humans
- Its plasma levels increase during the development of obesity
- visfatin is reported to exert insulin-mimetic effects to lower plasma glucose levels

Adipose tissue and adipokines: for better or worse.

- leptin and adiponectin both exert an insulin-sensitizing effect, at least in part, by favoring tIssue fatty-acId oxIdation through activation of AMP-activated kinase
- In obesity, insulin resistance has been linked to leptin resistance and decreased plasma adiponectin.
- In obesity, increased production of most adipokines impacts on multiple functions such as appetite and energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and haemostasis, all of which are linked with cardiovascular disease

How Obesity Causes Disease: The Fat Cell – A Multiendocrine Organ

FFA=free fatty acid; PAI-1=plasminogen activator inhibitor-1; TNF-α=tumor necrosis factor alpha; IL-6=interleukin 6

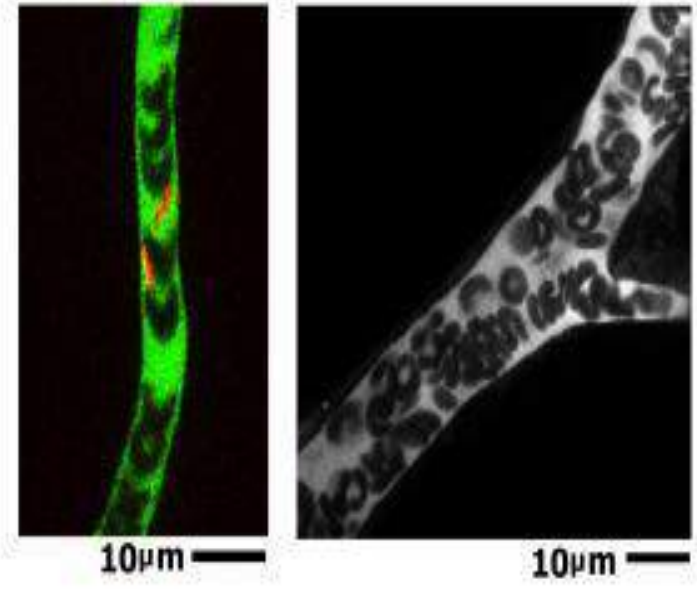
Slide: After Dr. G. Bray

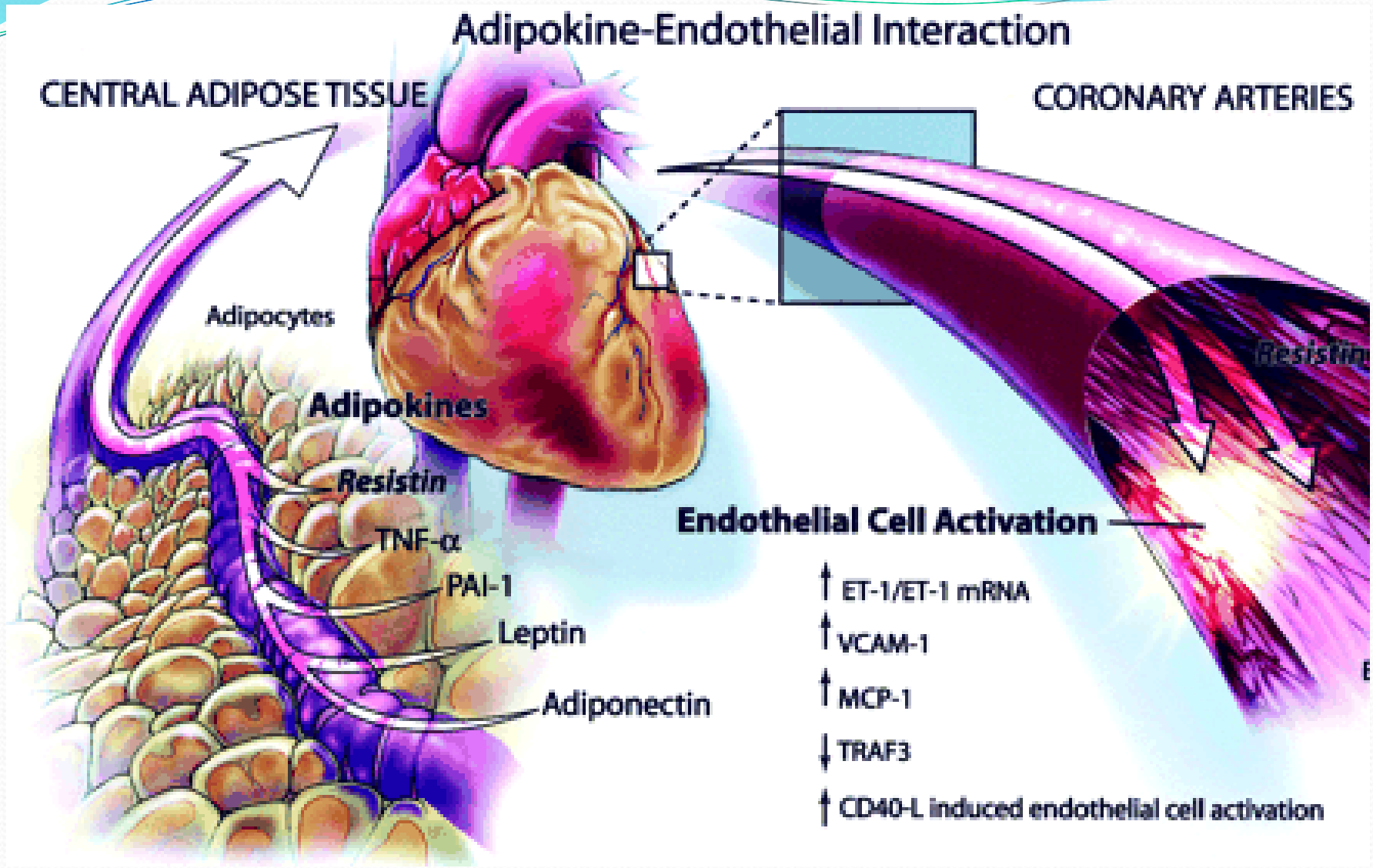
Inflamation and metabolic syndrome

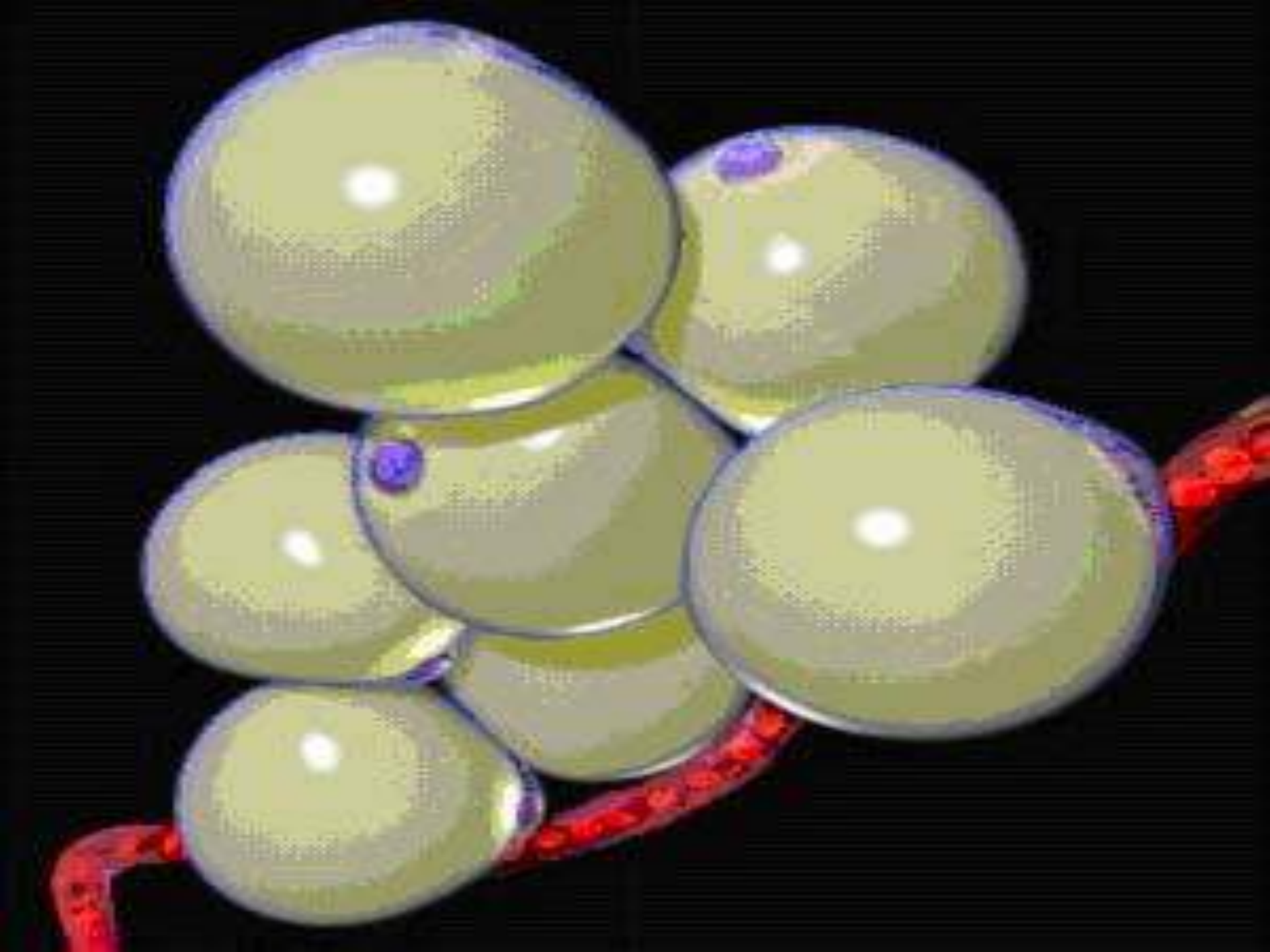
- **Visceral Fat Adipokine Secretion Is Associated With Systemic Inflammation in Obese Humans**
- hypothesis that visceral fat promotes systemic inflammation by secreting inflammatory adipokines into the portal circulation that drains visceral fat
- Adipose tissue expresses cytokines, e.g., tumor necrosis factor (TNF)1 and interleukin-6, which induce cachexia, insulin resistance, diabetes, and lipid abnormalities

Inflamation in adipose tissue

- — Individuals who are obese are at increased risk of developing a combination of medical disorders associated with type 2 diabetes and heart disease known as the metabolic syndrome

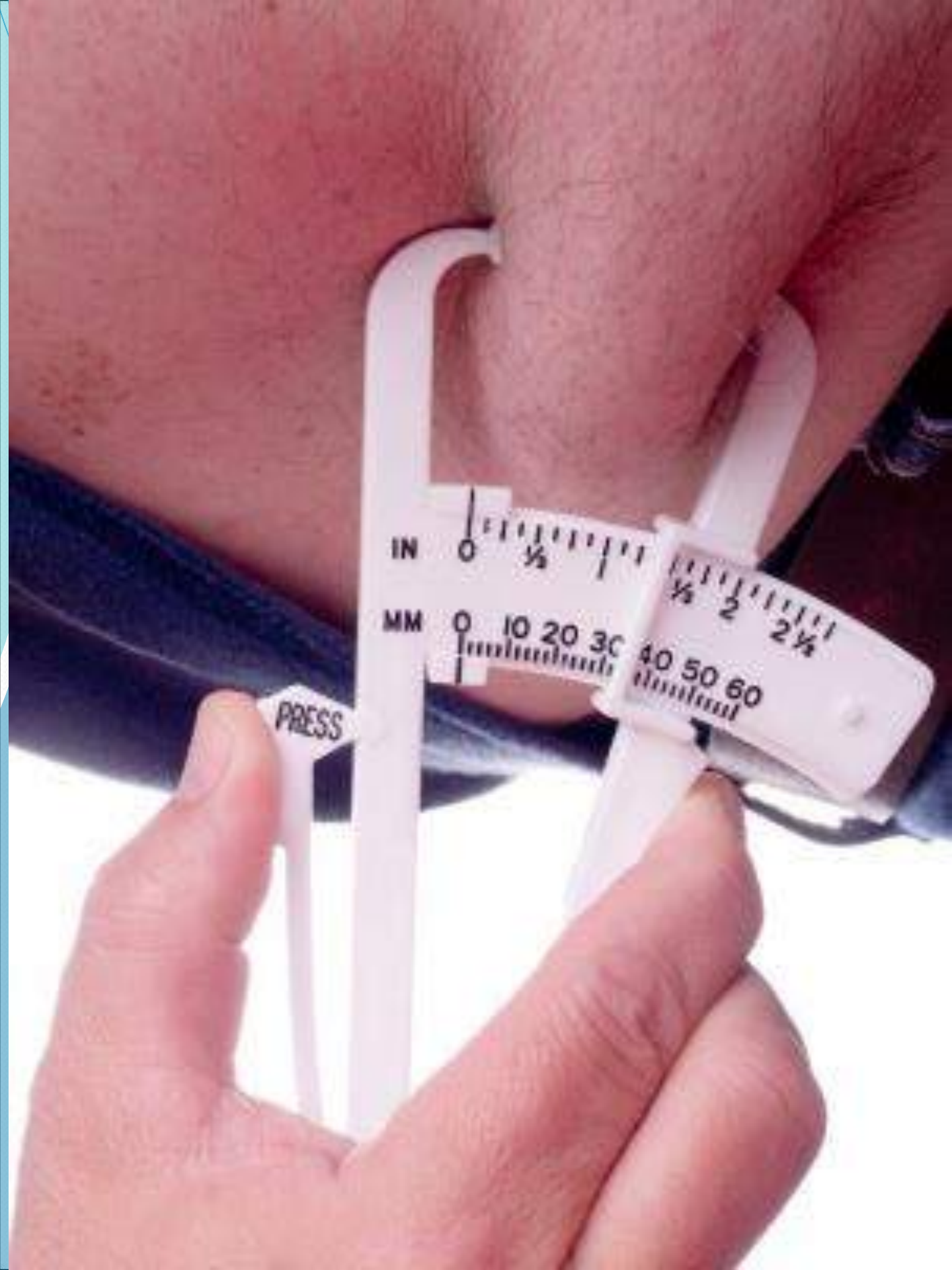



Adipokine-Endothelial Interaction
CENTRAL ADIPOSE TISSUE
CORONARY ARTERIES
Adipocytes
Adipokines
Resistin
TNF-α
PAI-1
Leptin
Adiponectin
Endothelial Cell Activation
↑ ET-1/ET-1 mRNA
↑ VCAM-1
↑ MCP-1
↓ TRAF3
↑ CD40-L induced endothelial cell activation



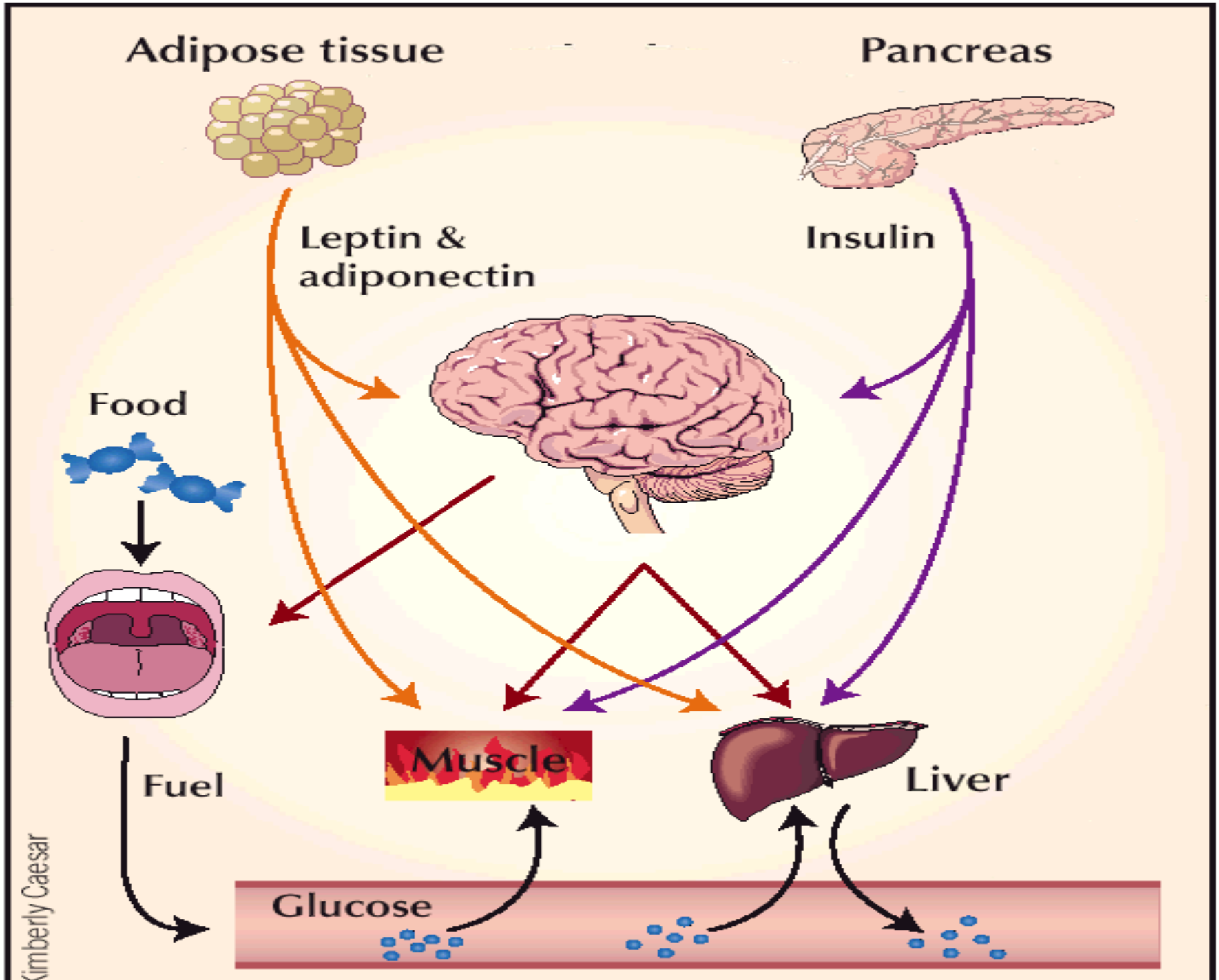
Obesity

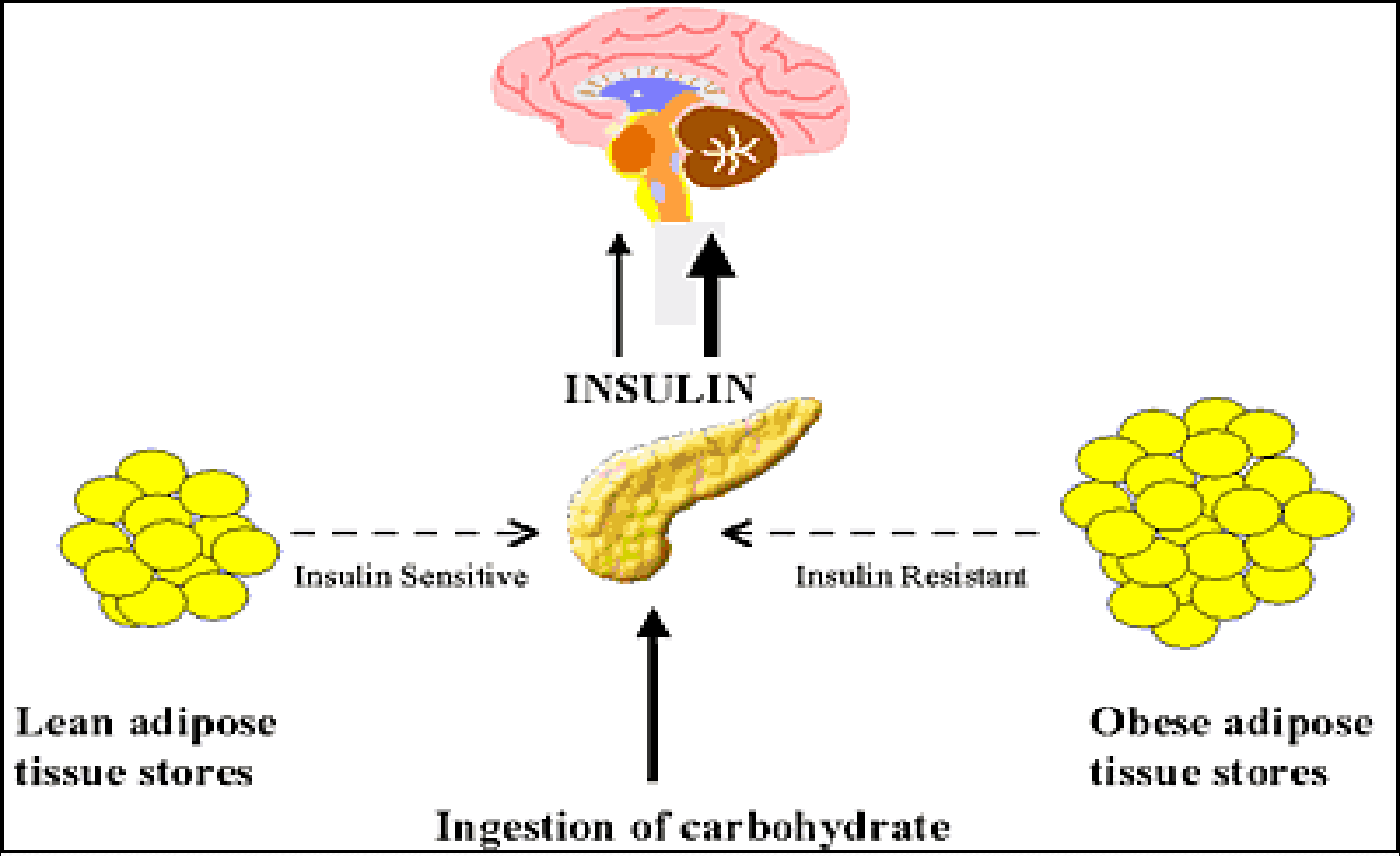
- **Obesity** represents a very complex disease, concerns all social classes and people at any age, even children. The percentage of people suffering from obesity is rapidly increasing, the disease thus being regarded as one of the most severe health hazards of the century.
- Obesity leads to a number of severe dysfunctions, such as hypertension, type 2 diabetes, cardiovascular diseases, stroke, orthopaedic disorders, and psychosocial complications.
- **Adiponectin, Leptin, Resistin, CRP, PAI-1, OPG, MPO, Iso-Insulin, IL-6, IL-18, TNF-alpha, sCD40L, sICAM-1, MCP-1, NGF, sTNF-R1**
- large number of endocrine, inflammatory, neural, and cell-intrinsic pathways have been shown to be dysregulated in obesity.


IN
0
½
1
½
1
2
2½
MM
0
10
20
30
40
50
60
PRESS

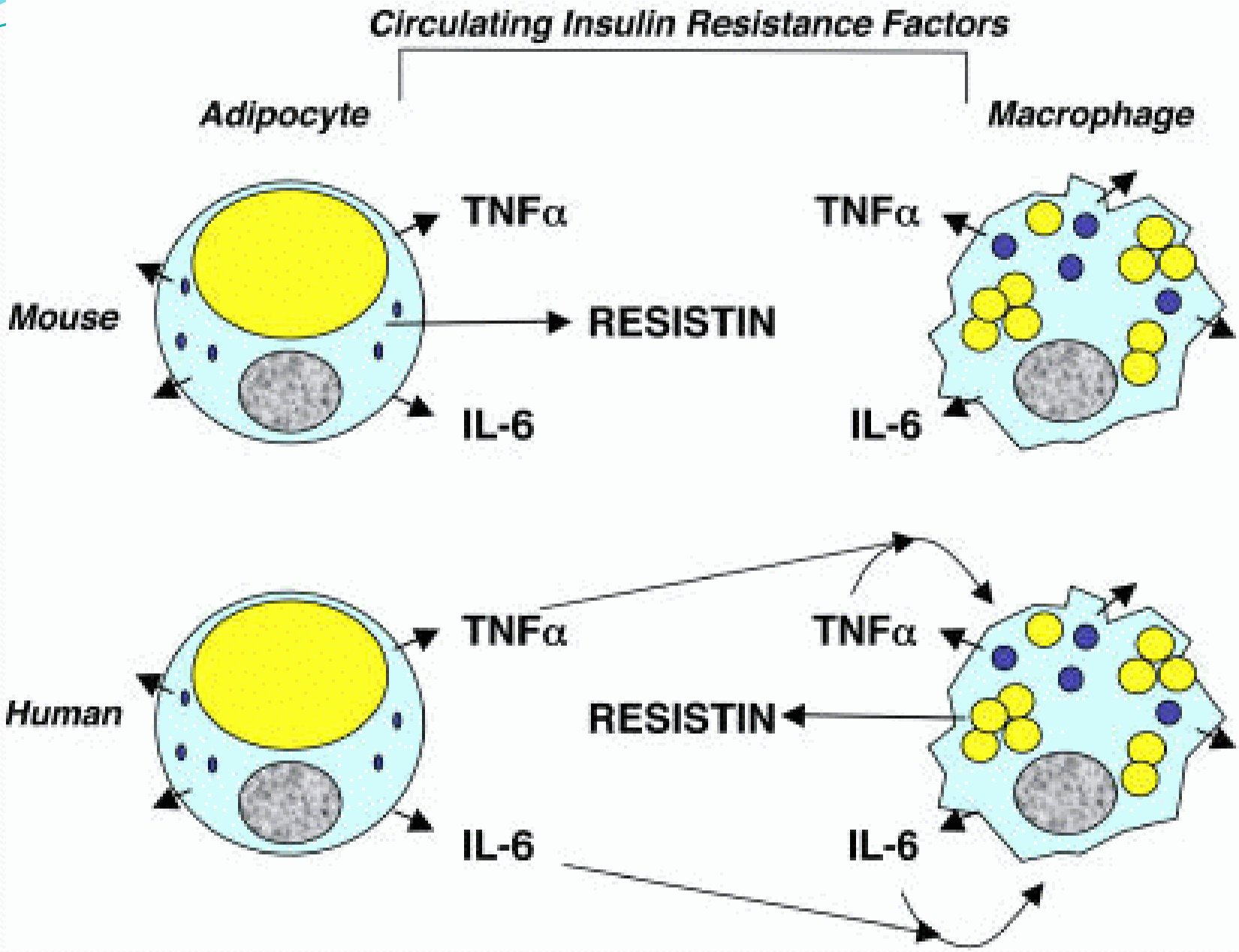
- **Obesity is a major risk factor for type II diabetes.**

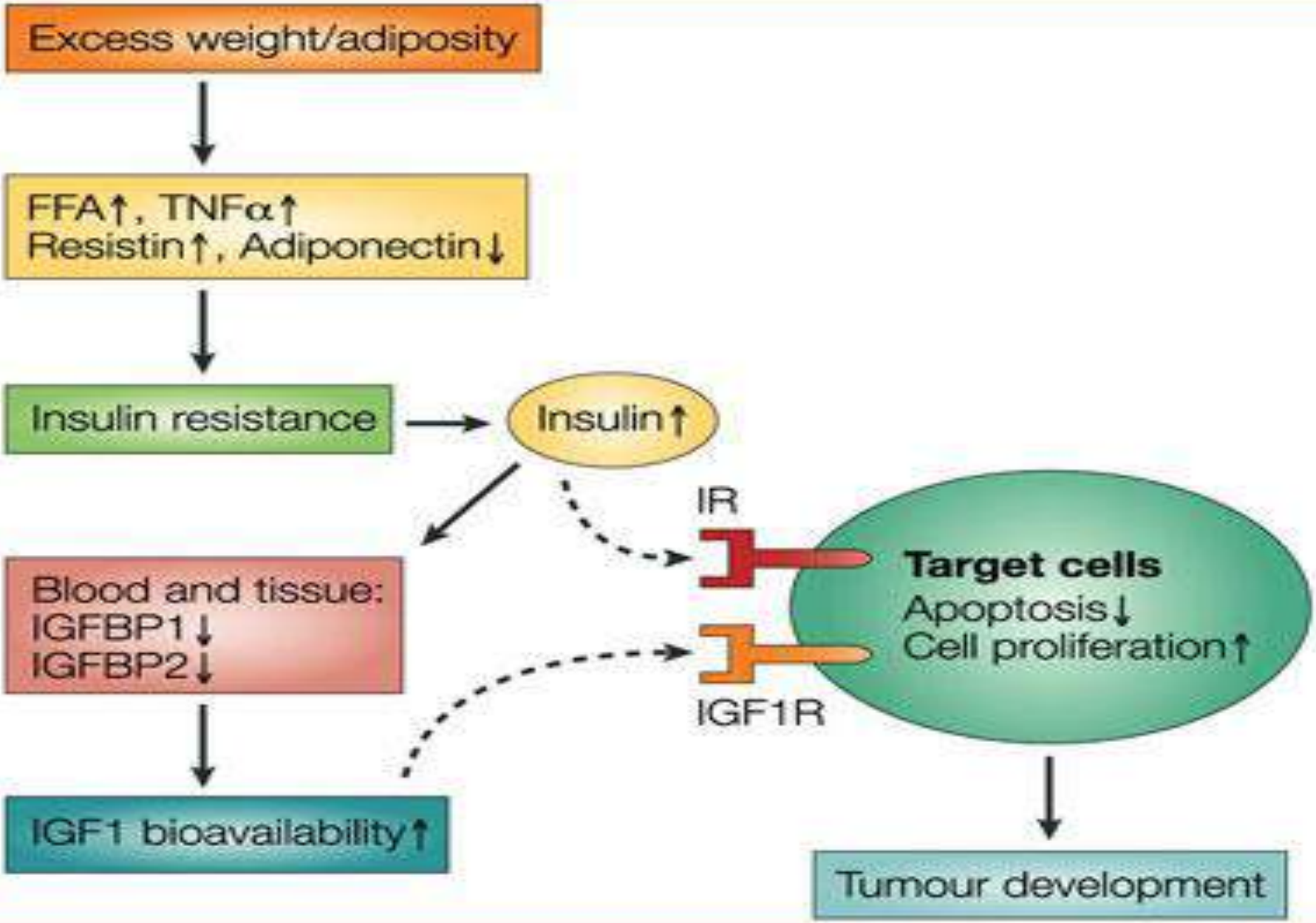
- Peripheral hormones from the pancreas and adipose tissue regulate both the level of glucose in the blood and the balance between energy intake and energy expenditure.
- Insulin secreted from the pancreas acts on muscle and liver to regulate glucose uptake and oxidation.
- The actions of insulin on muscle and liver are facilitated by adiponectin secreted from adipose mass.
- adiponectin also acts in the CNS to facilitate glucose disposal and increase total energy oxidation.
- Other hromone from adipose tissue such as leptin also control glucose and food intake via combined peripheral and central actions.

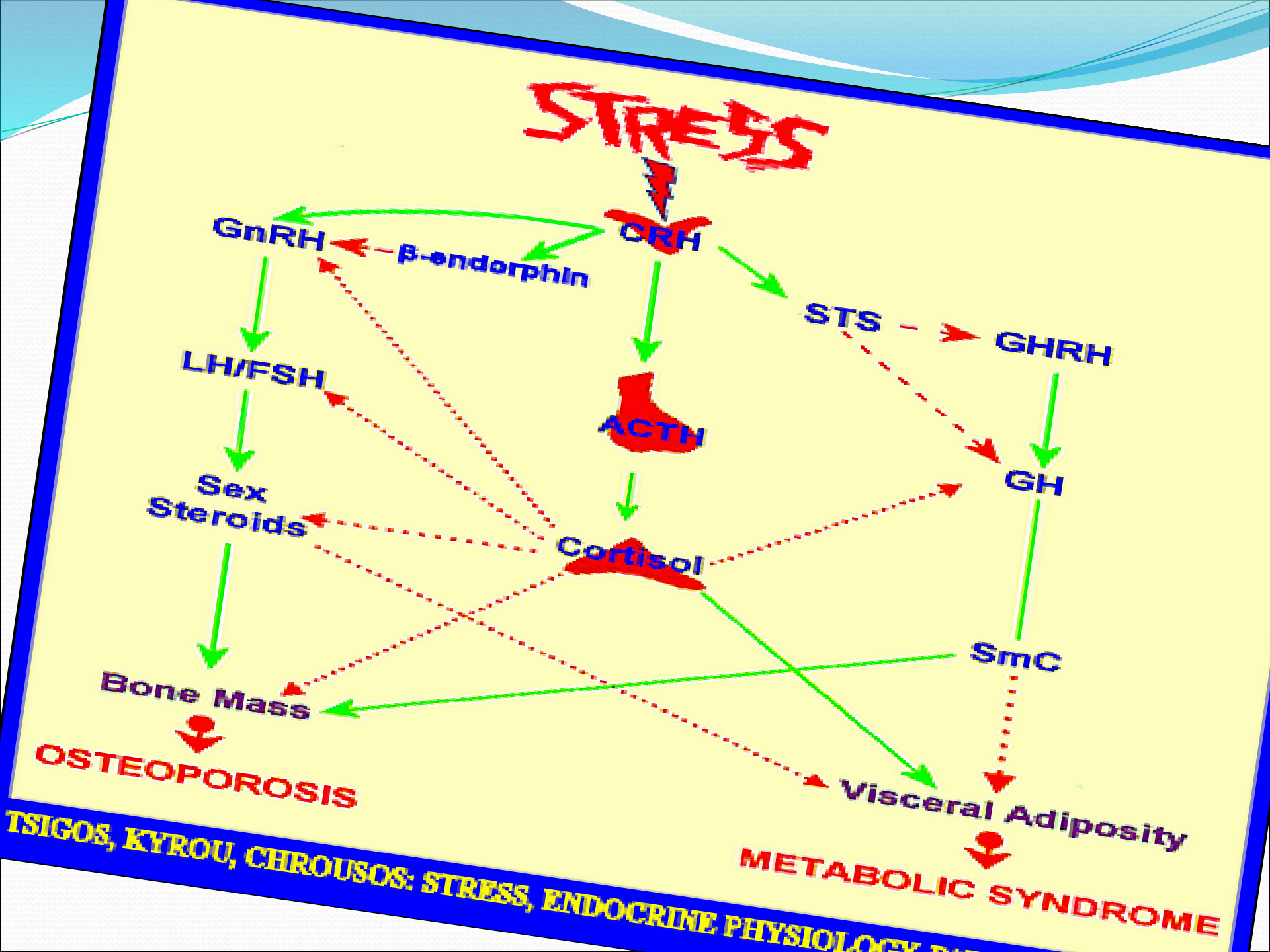

Adipose tissue
Pancreas
Leptin &
adiponectin
Insulin
Food
Muscle
Liver
Fuel
Glucose
Kimberly Caesar



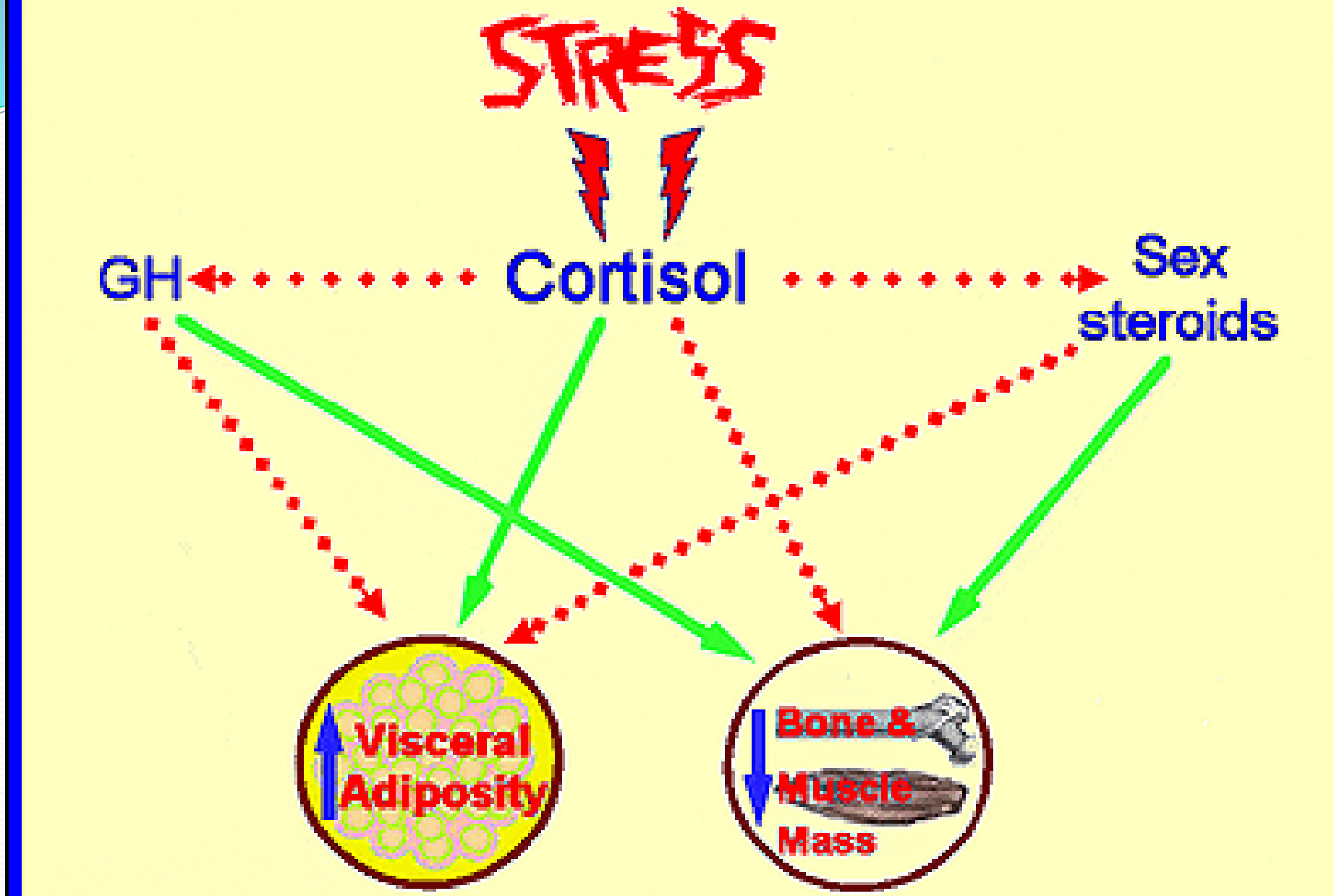
- Insulin signals the intake of nutrients and acts as measure of energy stores in the adipose tissue


Circulating Insulin Resistance Factors
Adipocyte
Macrophage
Mouse
TNFα
RESISTIN
IL-6
TNFα
IL-6
Human
TNFα
RESISTIN
IL-6
TNFα
IL-6

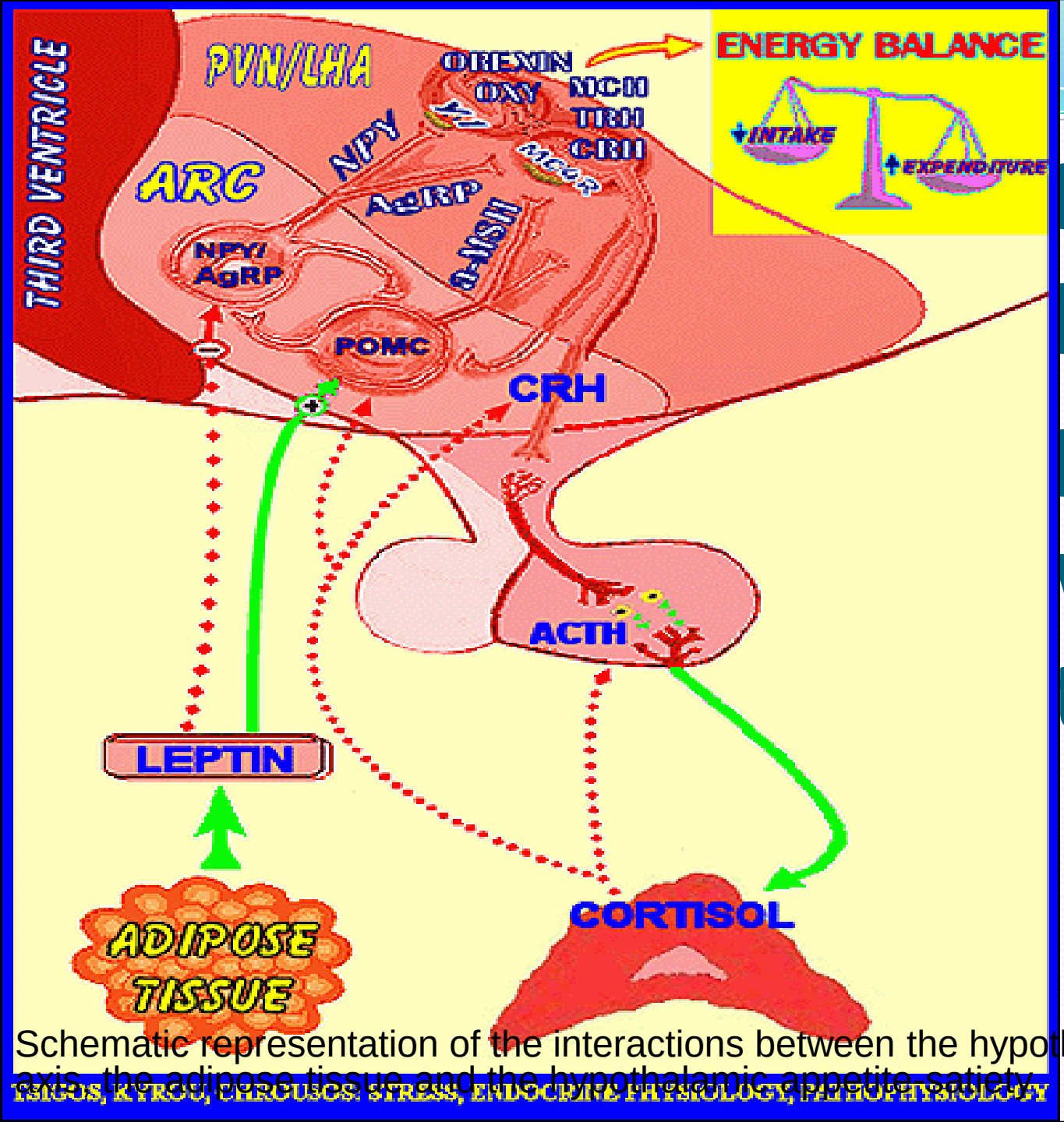



STRESS
CRH
GnRH
β-endorphin
STS
GHRH
LH/FSH
ACTH
GH
Sex Steroids
Cortisol
SmC
Bone Mass
OSTEOPOROSIS
Visceral Adiposity
METABOLIC SYNDROME
TSIGOS, KYROU, CHROUSOS: STRESS, ENDOCRINE PHYSIOLOGY

- Thus, glucocorticoids increase hepatic gluconeogenesis and plasma glucose concentration, induce lipolysis (although they favor abdominal and dorsocervical fat accumulation)
- In addition to their direct catabolic actions, glucocorticoids also antagonize the beneficial anabolic actions of GH, insulin and sex steroids on their target tissues (85). This shift of the metabolism toward a catabolic state by the activated HPA axis normally



TSIGOS, KYROU, CHROUSOS: STRESS, ENDOCRINE PHYSIOLOGY, PATHOPHYSIOLOGY



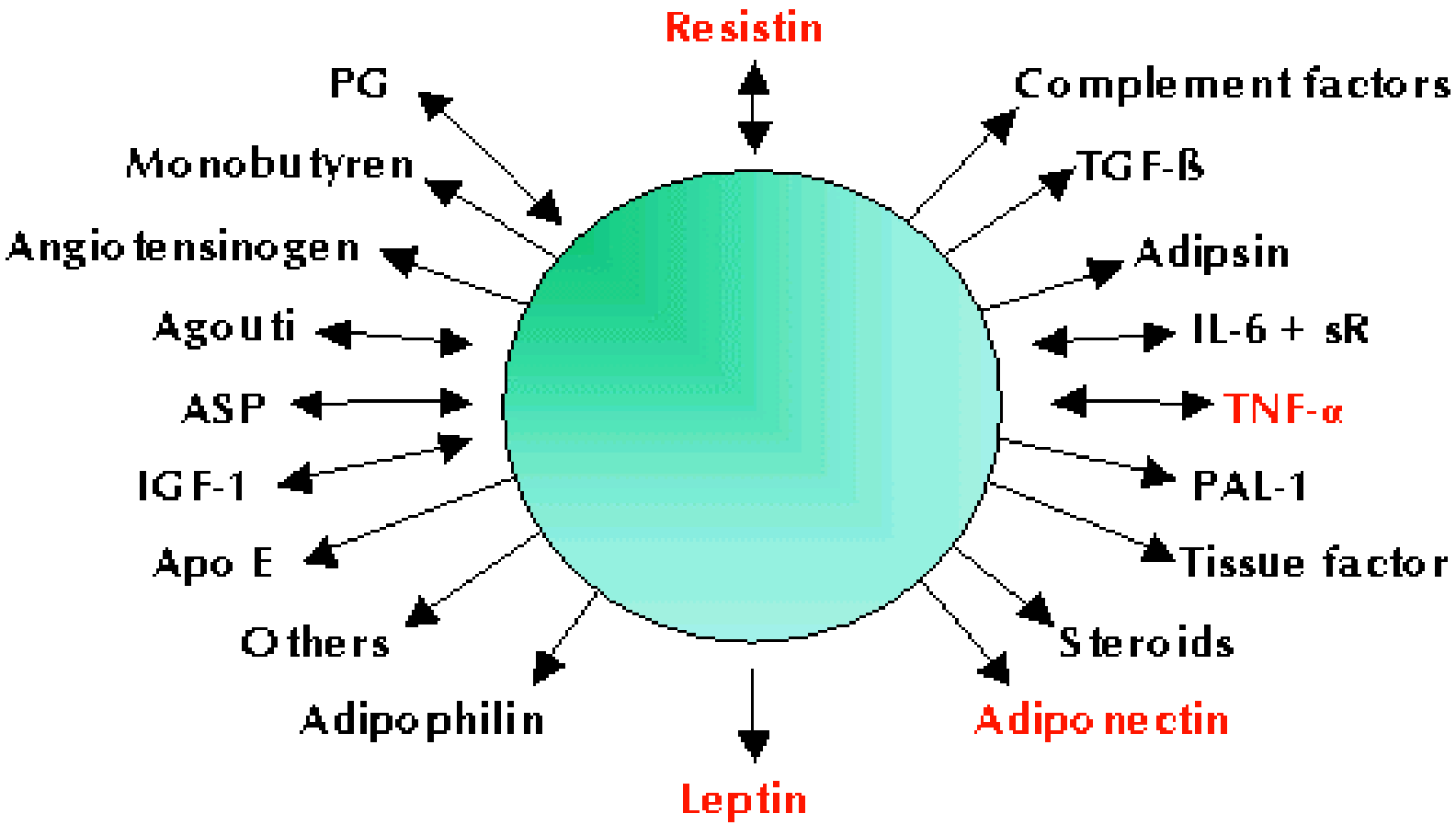
Fat hormones pull their weight in the CNS

Schematic representation of the interactions between the hypothalamic-pituitary-adrenal axis, the adipose tissue and the hypothalamic appetite satiety

Flow chart

- *Appetite-satiety centers - Appetite Regulation*

Adipose Tissue as an Endocrine Organ



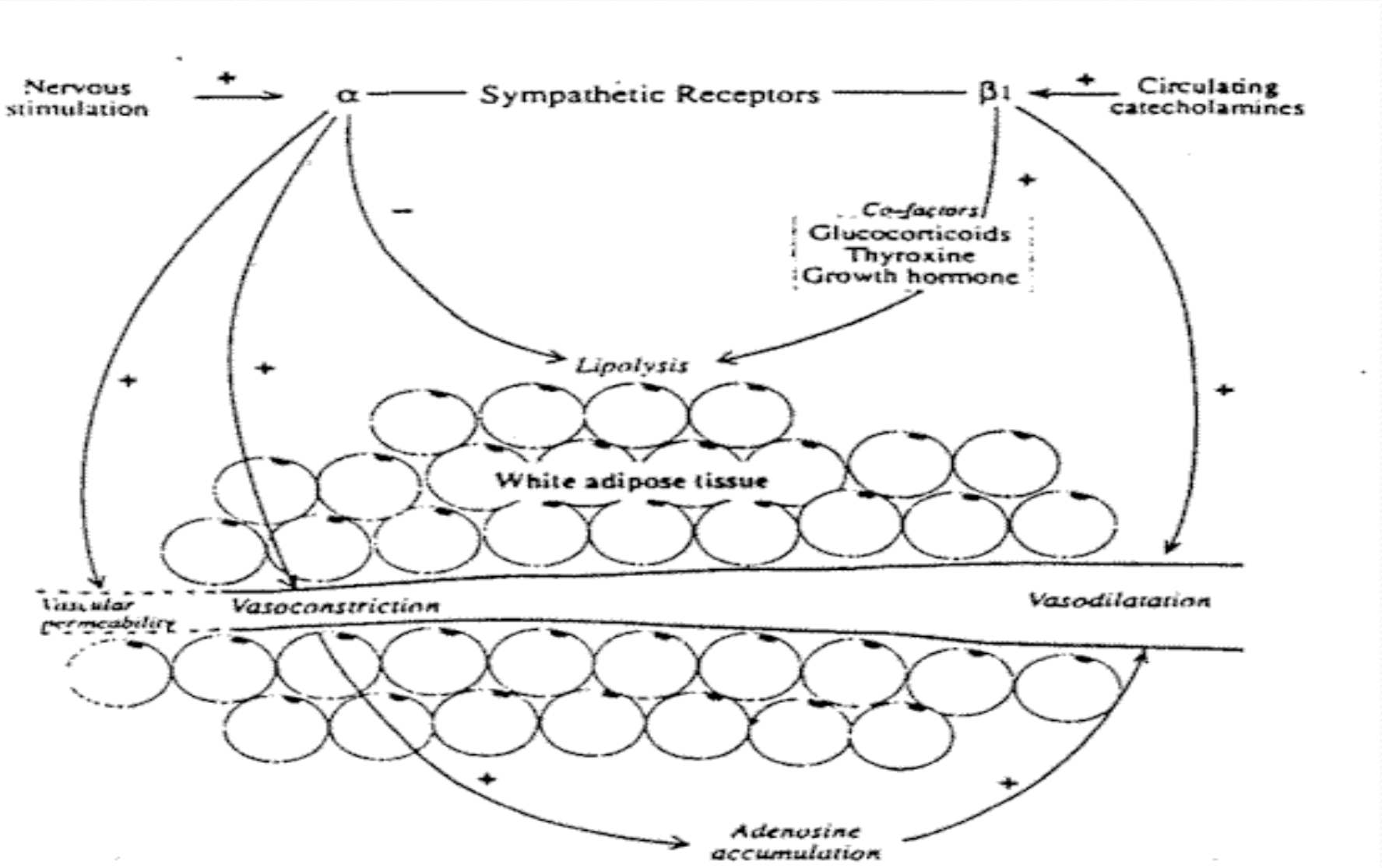
Cema Fridbeck, Obesity Matters, 2001,4, 16-19.

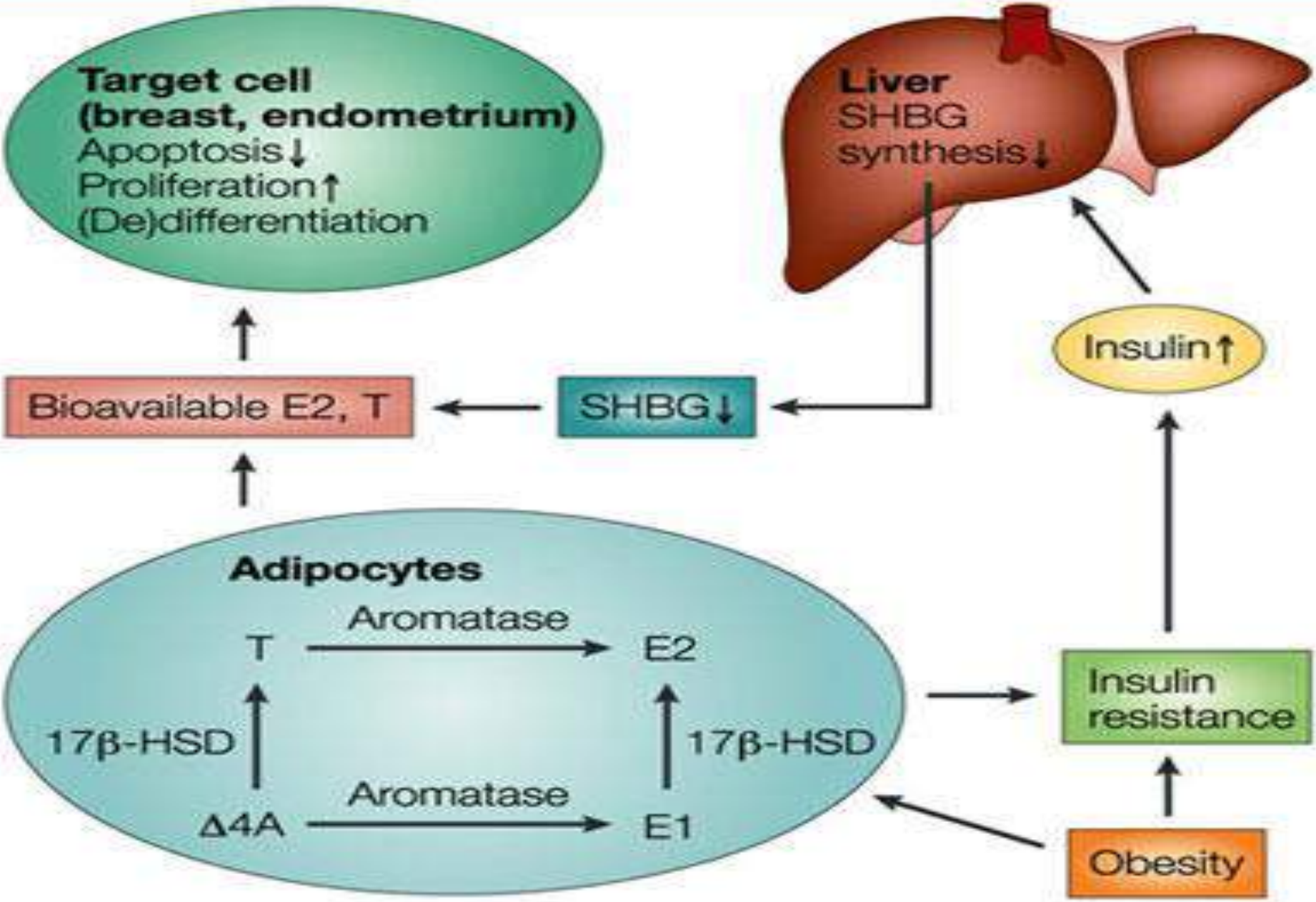
Question slide

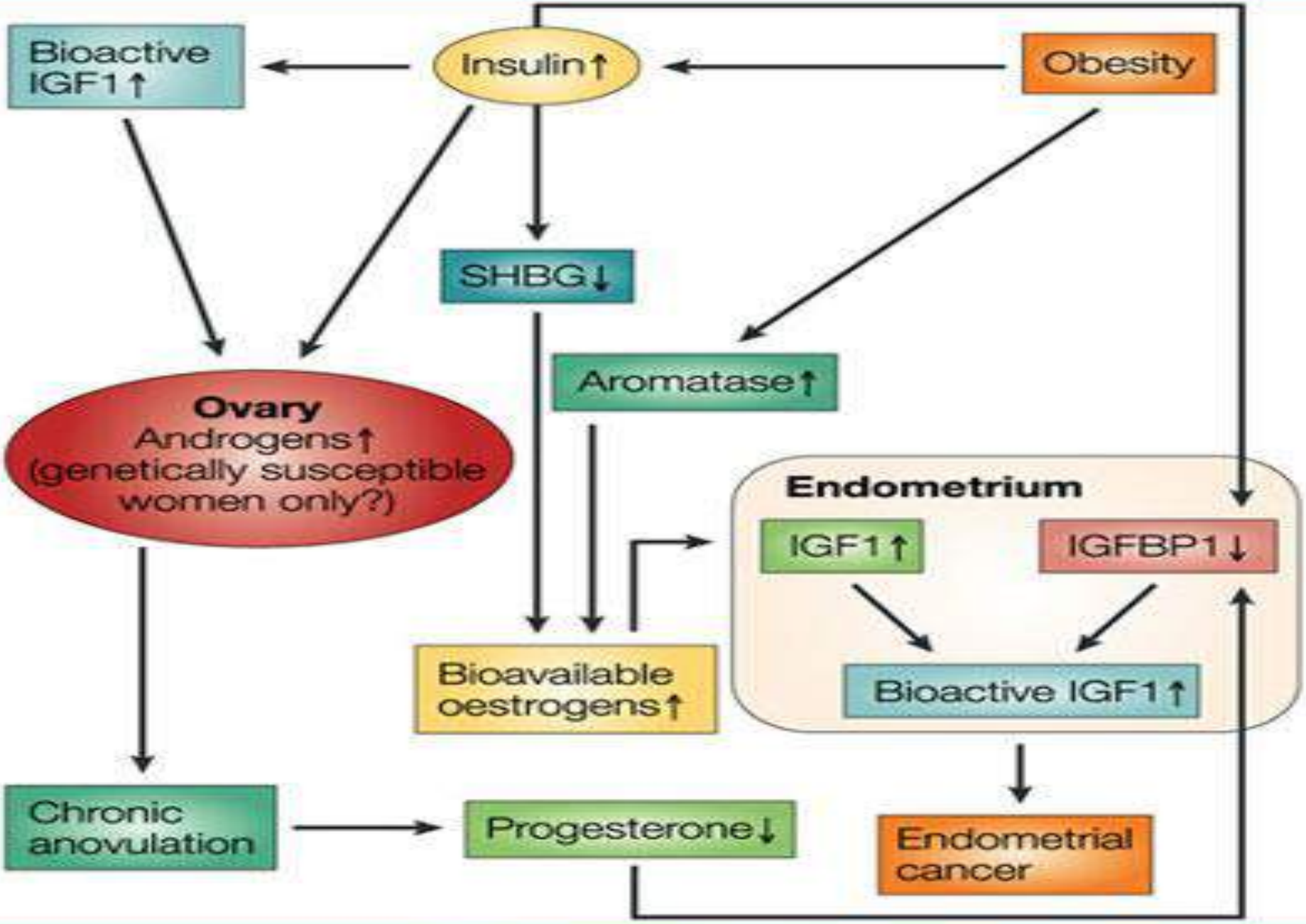
- Factors that predispose individuals to local or generalized hypertrophy of adipose tissue are still poorly defined, but there is evidence that the autonomic nervous system may not be functioning fully in obese subjects, either as a primary or secondary phenomenon

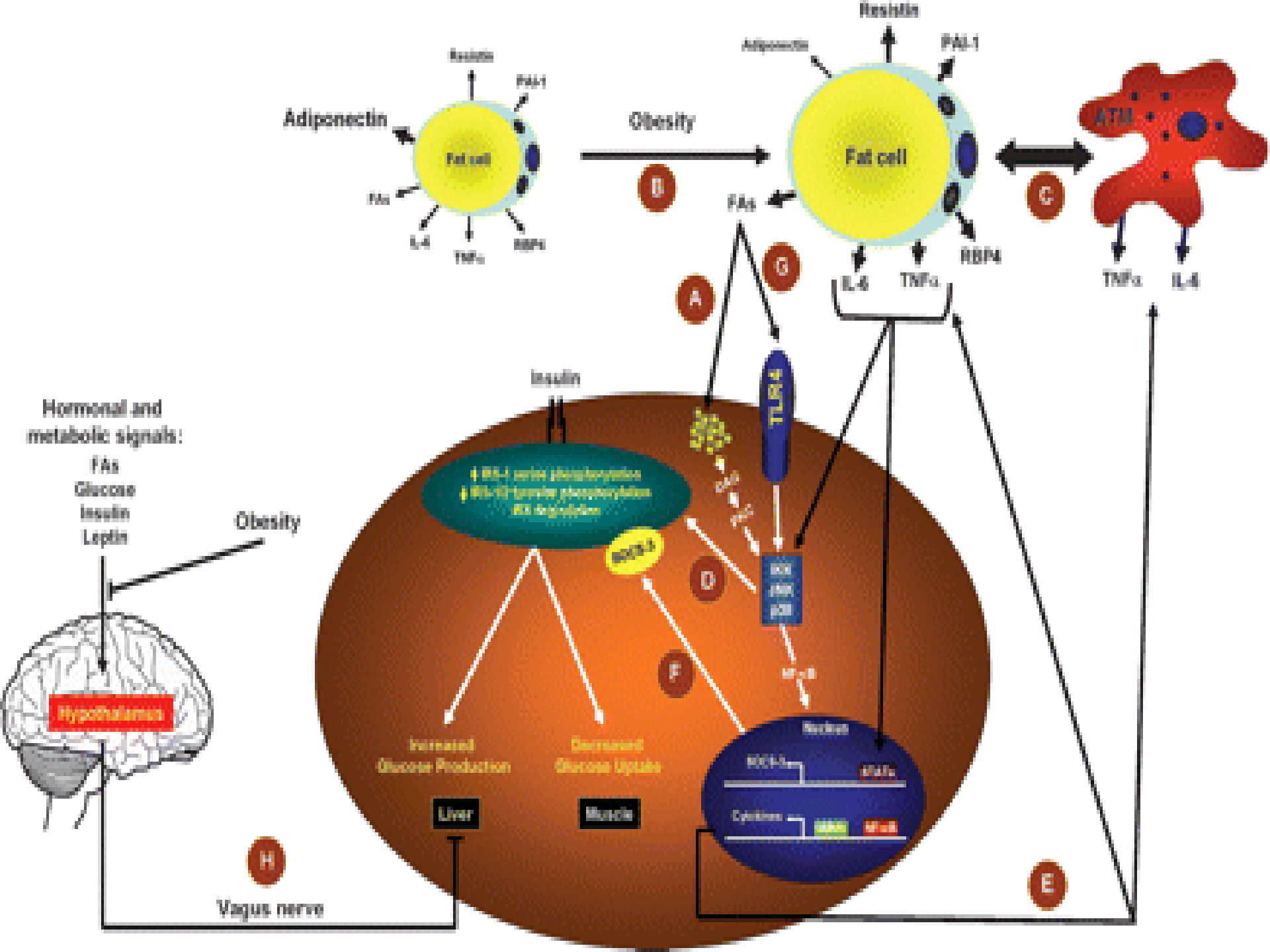
- Adipose tissue produces several proteins of the renin angiotensin system including renin, angiotensin, angiotensin I, angiotensin II, and angiotensin-converting enzyme
- angiotensin II is important in blood pressure regulation, adipose tissue production may be the link between obesity and hypertension.

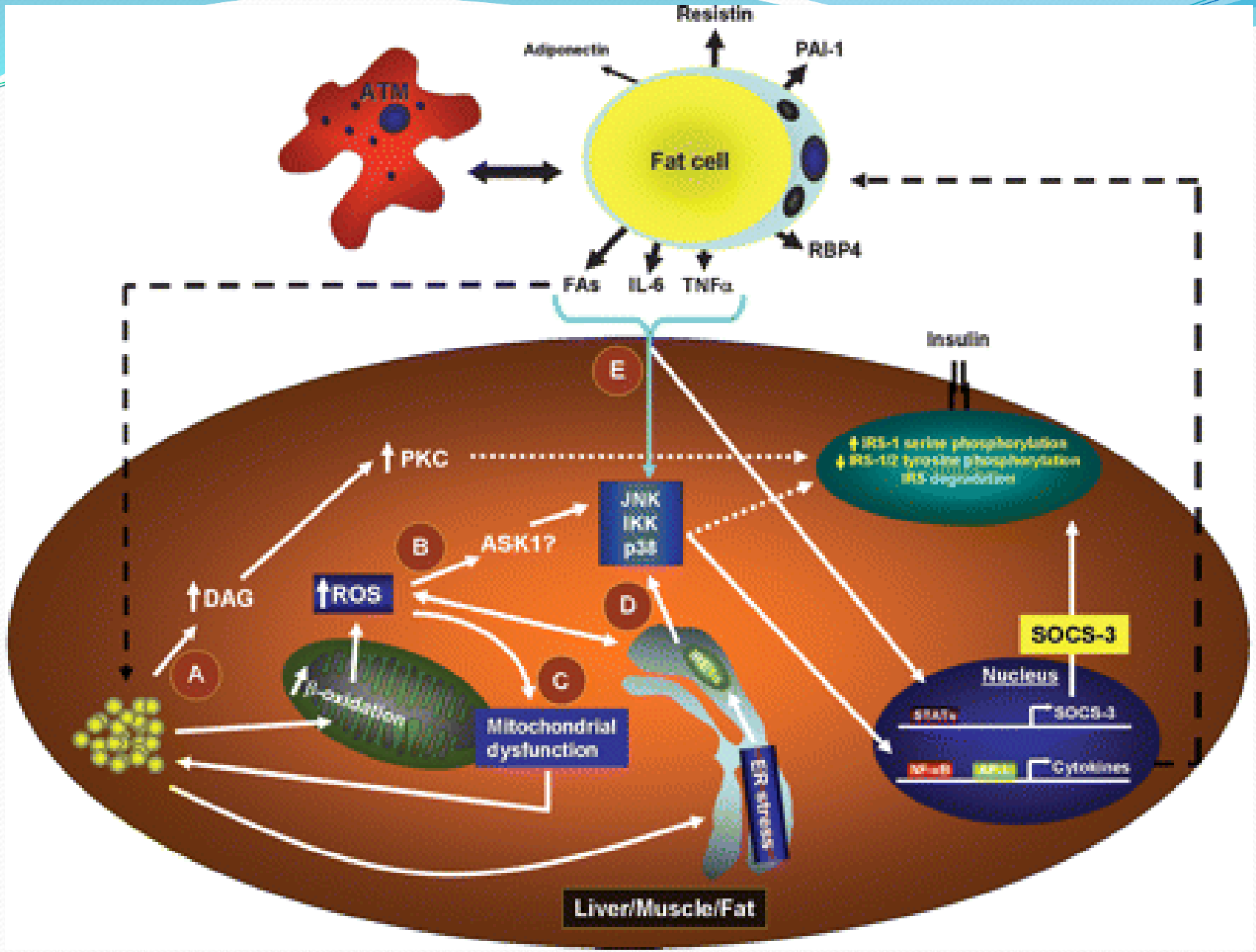
Fig. 6-1. The metabolic and vascular effects of sympathetic receptor stimulation in

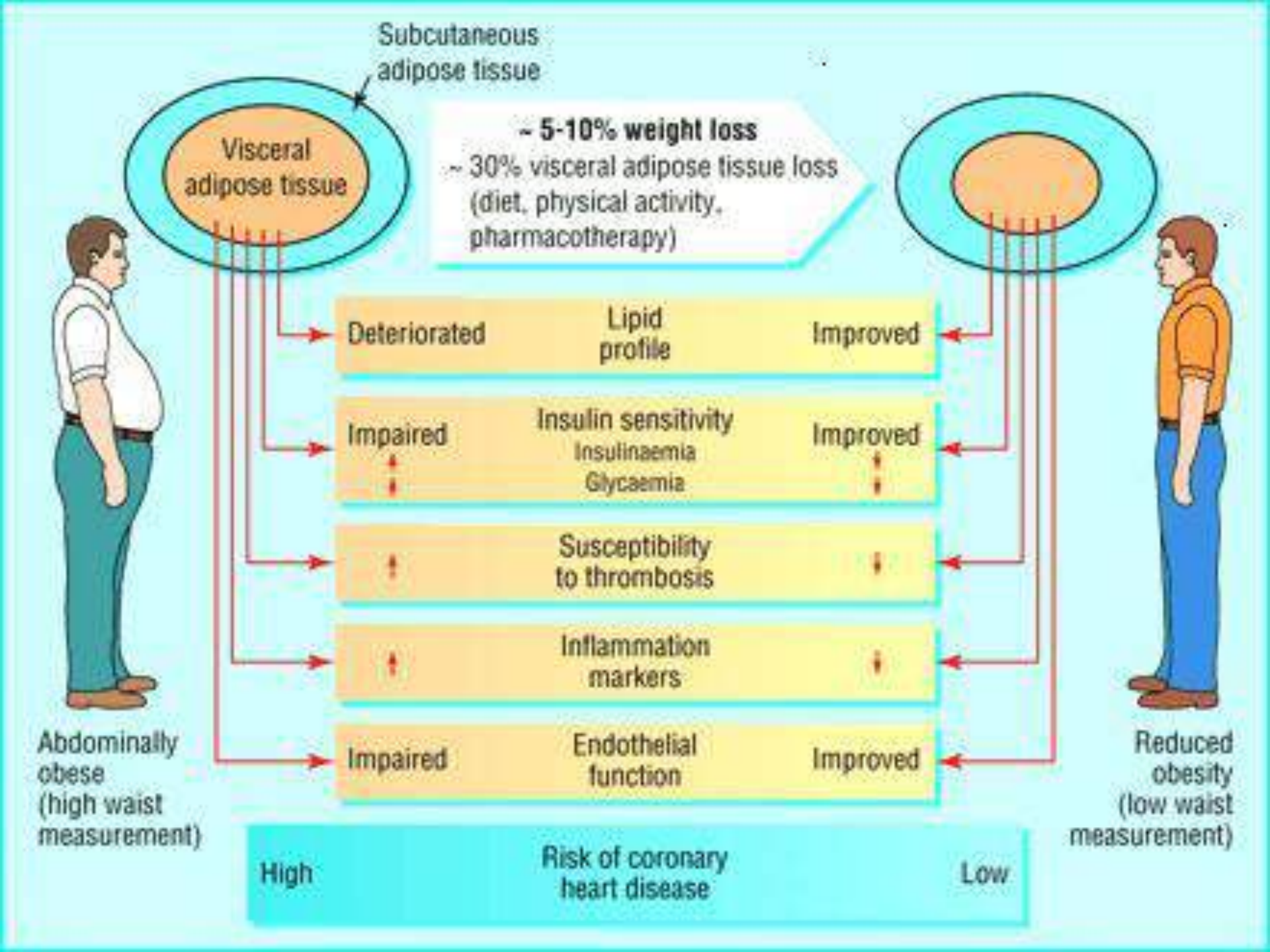







Resistin
PAI-1
Adiponectin
Fat cell
FAs
IL-6
TNFα
RBP4
Obesity
B
Resistin
Adiponectin
PAI-1
Fat cell
FAs
RBP4
IL-6
TNFα
C
ATM
TNFα
IL-6
A
G
Insulin
TLR4
Hormonal and metabolic signals:
FAs
Glucose
Insulin
Leptin
Obesity
Hypothalamus
D
F
Increased Glucose Production
Decreased Glucose Uptake
Liver
Muscle
Nucleus
Cytokines
H
Vagus nerve
E


Resistin
Adiponectin
PAI-1
ATM
Fat cell
RBP4
FAs
IL-6
TNFα
Insulin
E
PKC
JNK
IKK
p38
IRS-1 serine phosphorylation
IRS-1/2 tyrosine phosphorylation
IRS degradation
B
ASK1?
DAG
ROS
D
SOCS-3
A
C
Nucleus
β-oxidation
Mitochondrial dysfunction
STAT
SOCS-3
NF-κB
MAPK
Cytokines
ER stress
Liver/Muscle/Fat


Subcutaneous adipose tissue
Visceral adipose tissue
~ 5-10% weight loss
~ 30% visceral adipose tissue loss (diet, physical activity, pharmacotherapy)
Deteriorated
Lipid profile
Improved
Impaired
Insulin sensitivity
Insulinaemia
Glycaemia
Improved
Susceptibility to thrombosis
Inflammation markers
Impaired
Endothelial function
Improved
Abdominally obese (high waist measurement)
Reduced obesity (low waist measurement)
High
Risk of coronary heart disease
Low

Leptin

Adipose Tissue as an Endocrine Organ