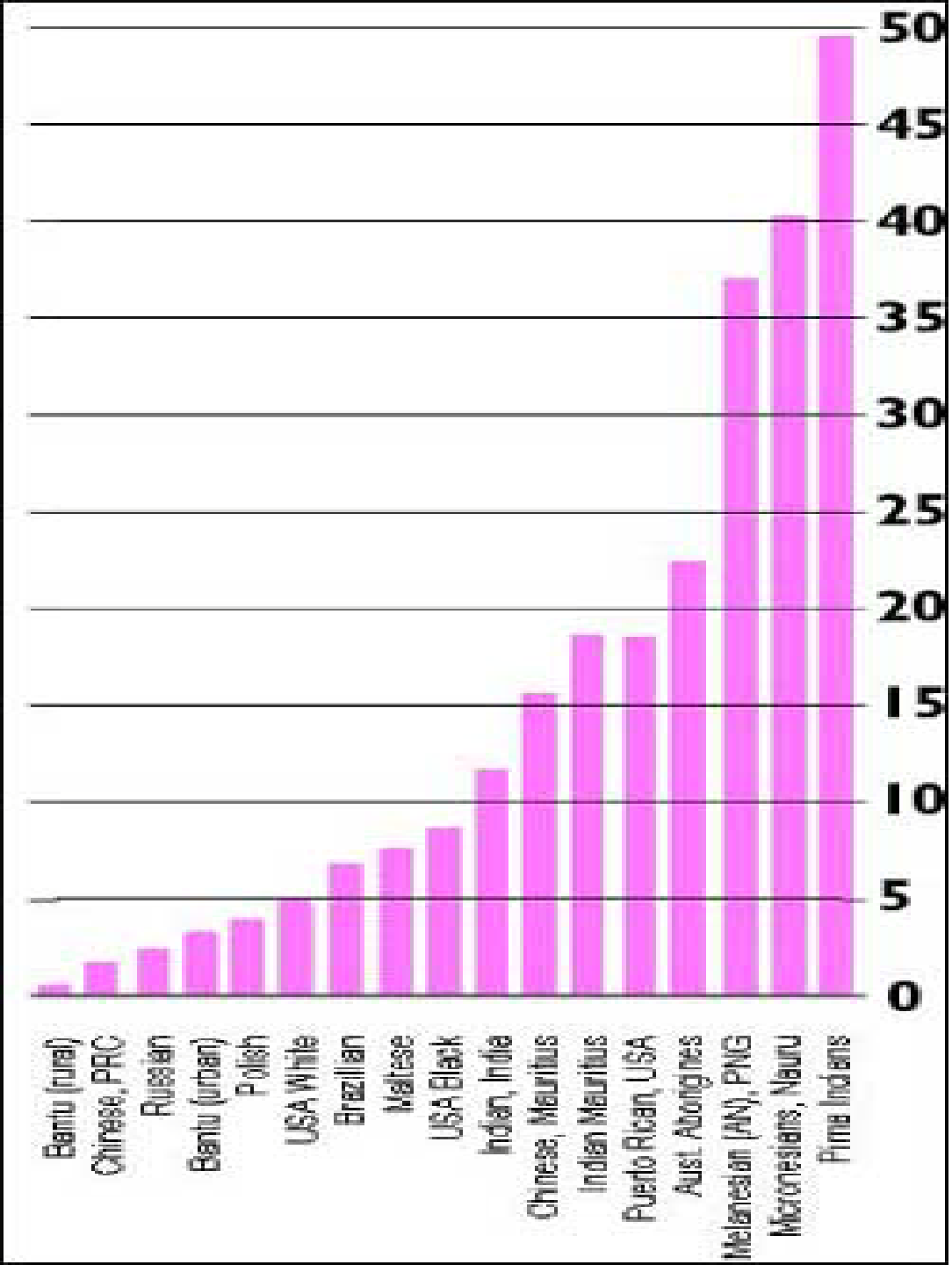

PPARγ

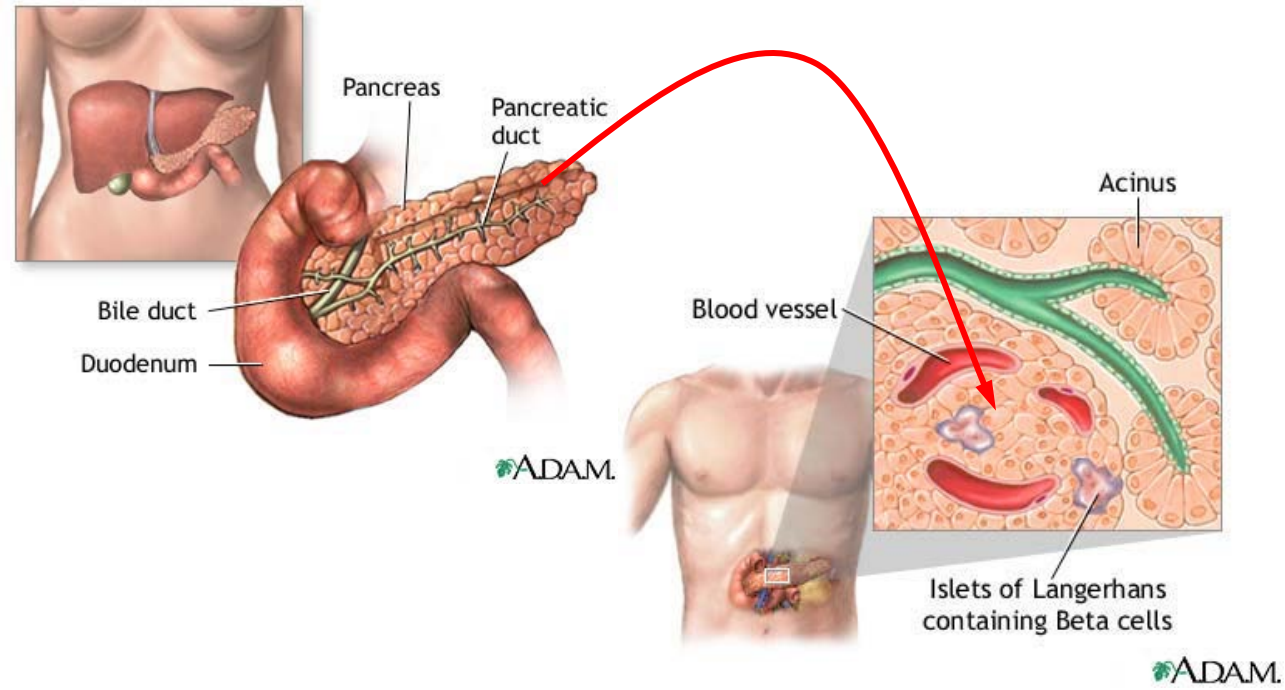


Diabetes

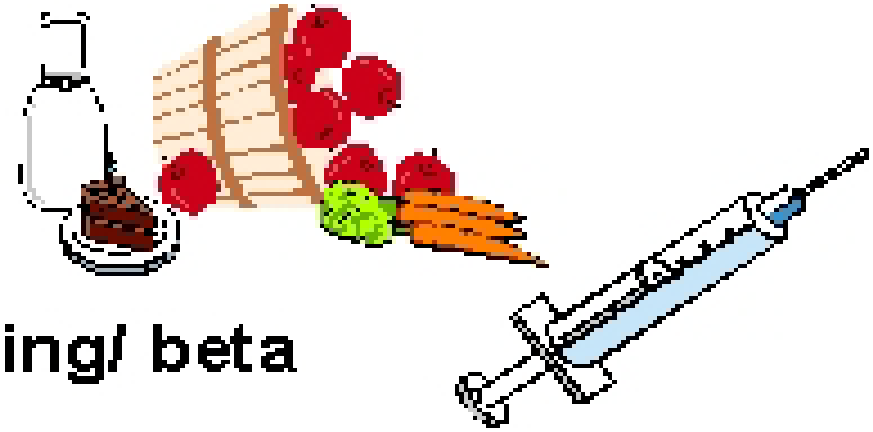
- **Diabetes mellitus is a chronic disease characterized by elevated blood sugars for months to years.**
- **Diabetes is characterized by either: (1) an inability of the pancreas to produce insulin (type 1 or insulin-dependent diabetes mellitus) or an inability of insulin to exert its normal physiological actions (type 2 or non-insulin dependent diabetes).**
- **Often recognized in patients by excessive urination, thirst, weight loss and/or a lack of energy. But diabetes is often silent and may exist for many years without the individual's noticing it.**
- **Tissues and organs which are vulnerable to the damaging effects of chronically high blood sugar levels are the eye, kidney, nerves and blood vessels.**

TYPE 1 DM

- Formerly IDDM :
  - insulin deficient
  - juvenile onset,
  - Origins
    - Autoimmune



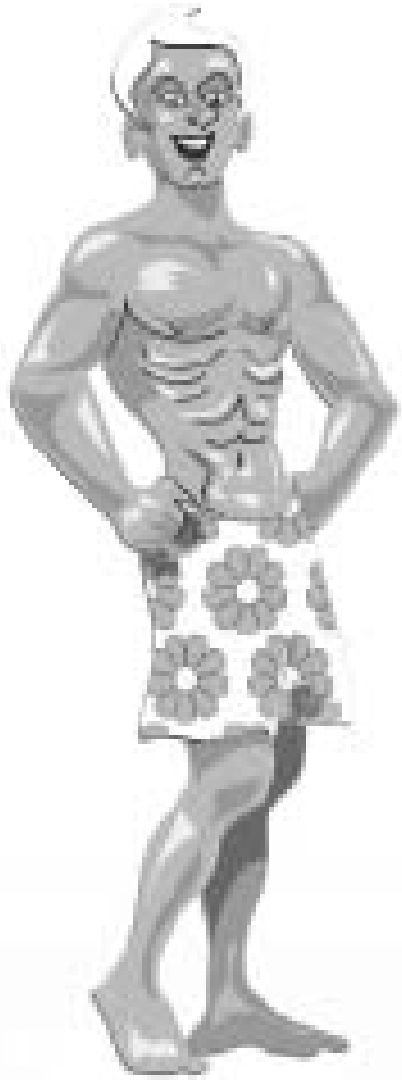
- pancreatic beta cell death



- insulin regimen/dietary planning/ beta cell or islet transplants

TYPE 2 DM

- Formerly NIDDM:
  - insulin RESISTANT
  - adult onset
  - genetic origins unclear, polygenic
  - associations with obesity
  - hyperinsulinemia followed by IDDM
  - insulin regimen, oral hypoglycemics, diet, exercise and weight loss



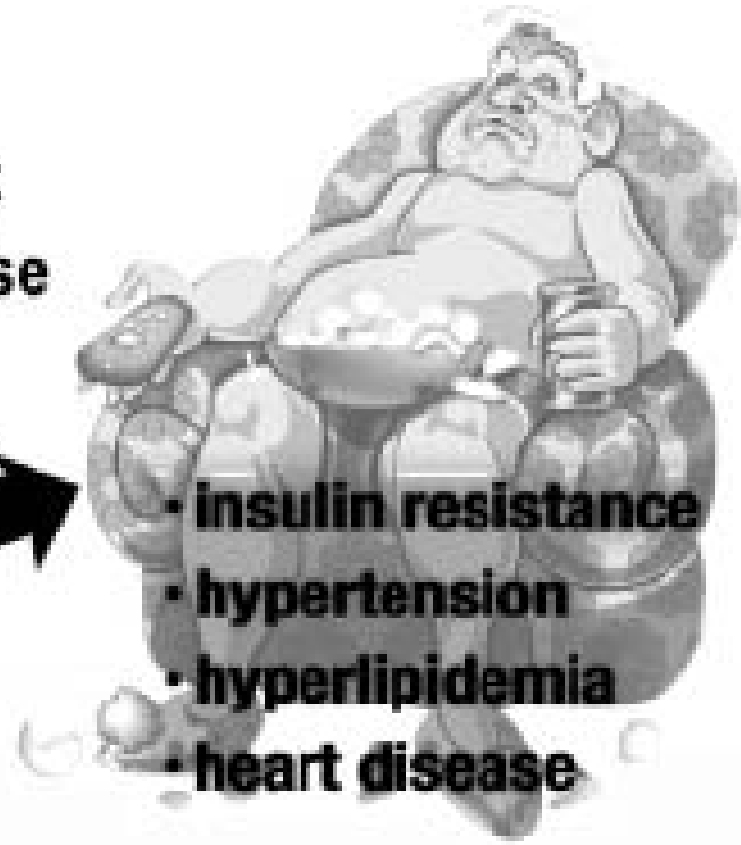
Exercise

Syndrome X

High fat diet

Poor exercise

Genetics

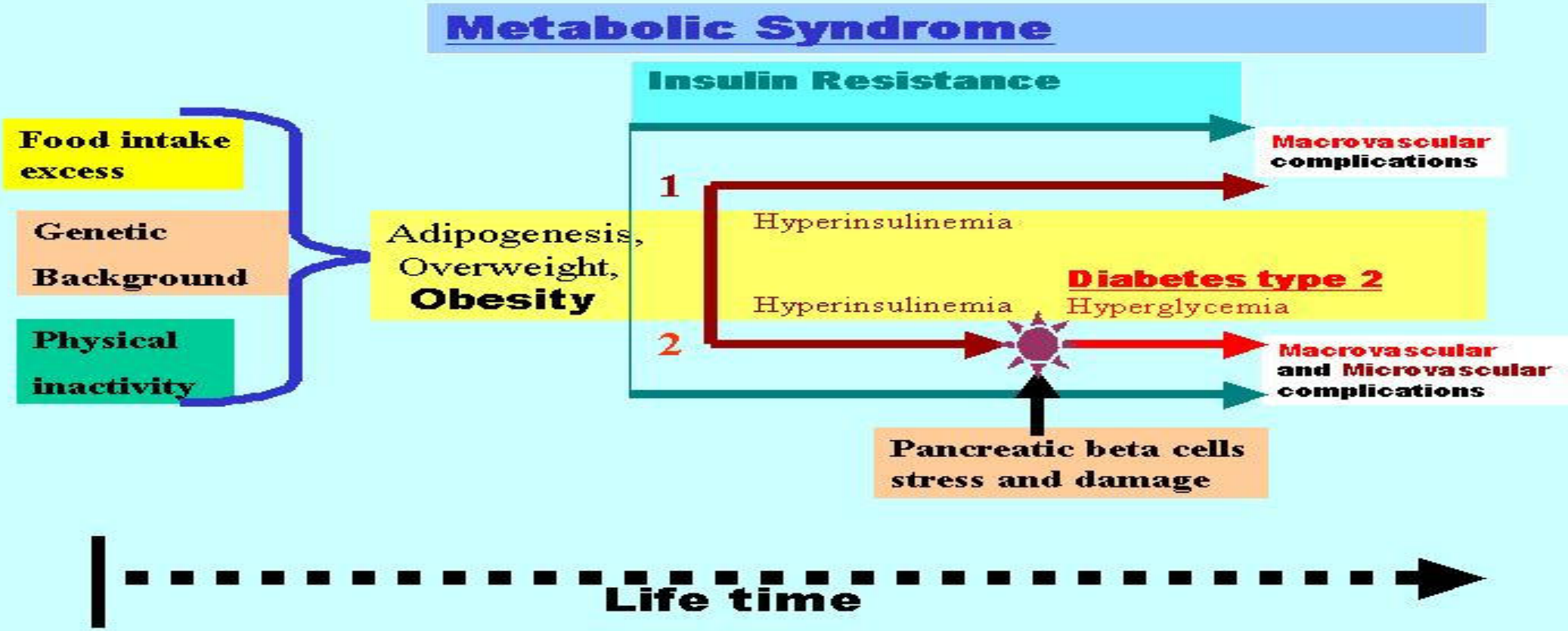


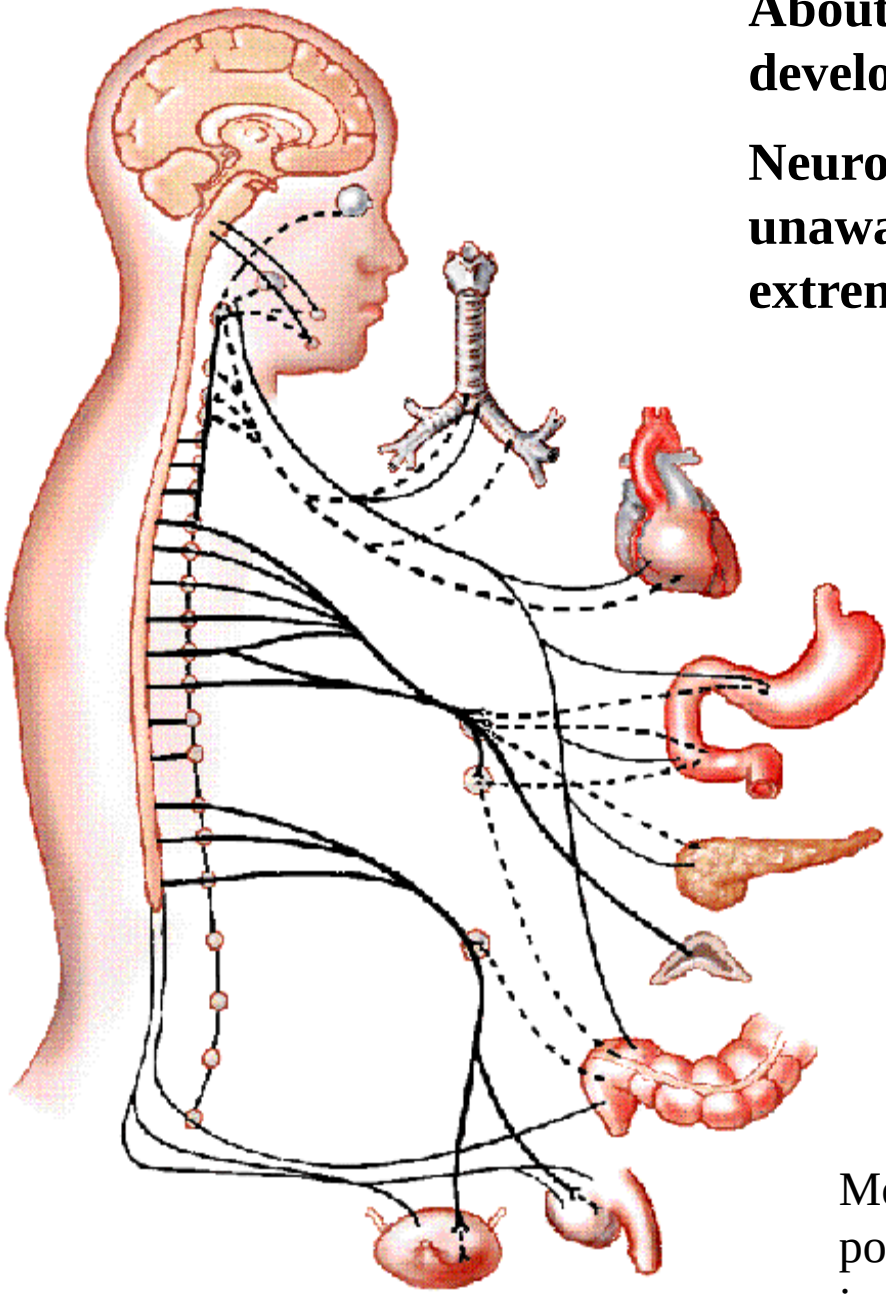
- insulin resistance
- hypertension
- hyperlipidemia
- heart disease

An insulin-resistant state is the key phase of metabolic syndrome-X:

* With preserved pancreatic β cells and insulin hypersecretion which can compensate for insulin resistance.

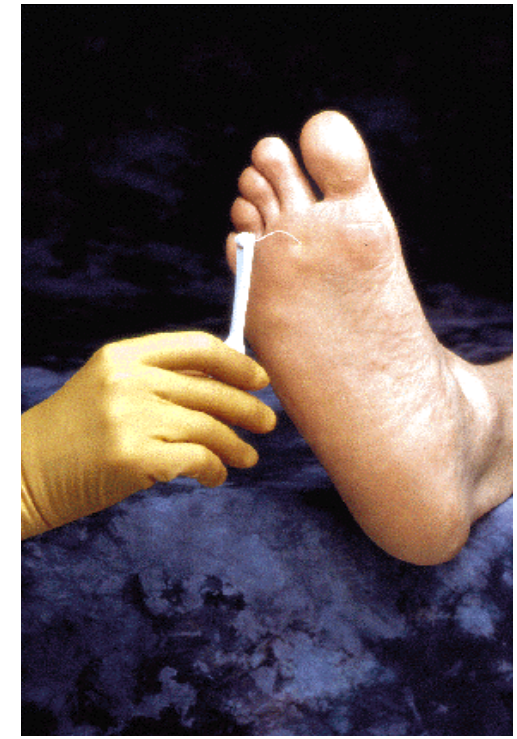
*With damage of pancreatic β cells leading to decrease of insulin secretion and to hyperglycemia (to type 2 diabetes).



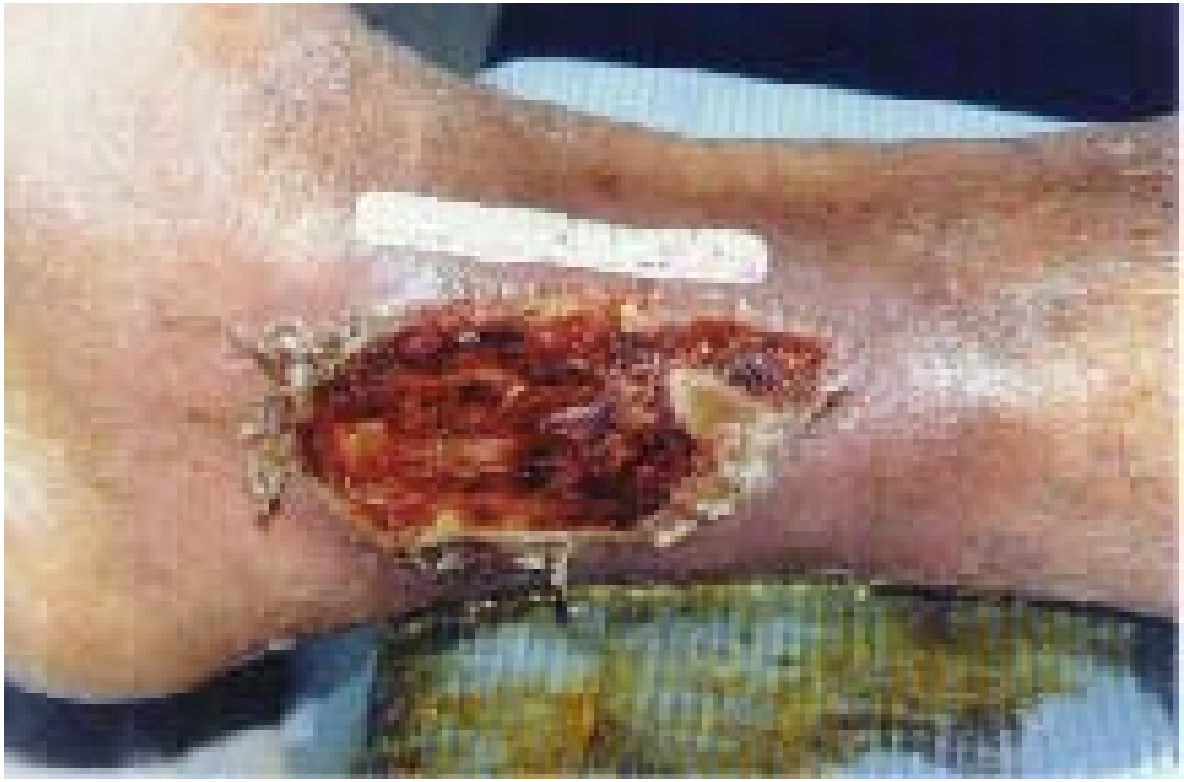


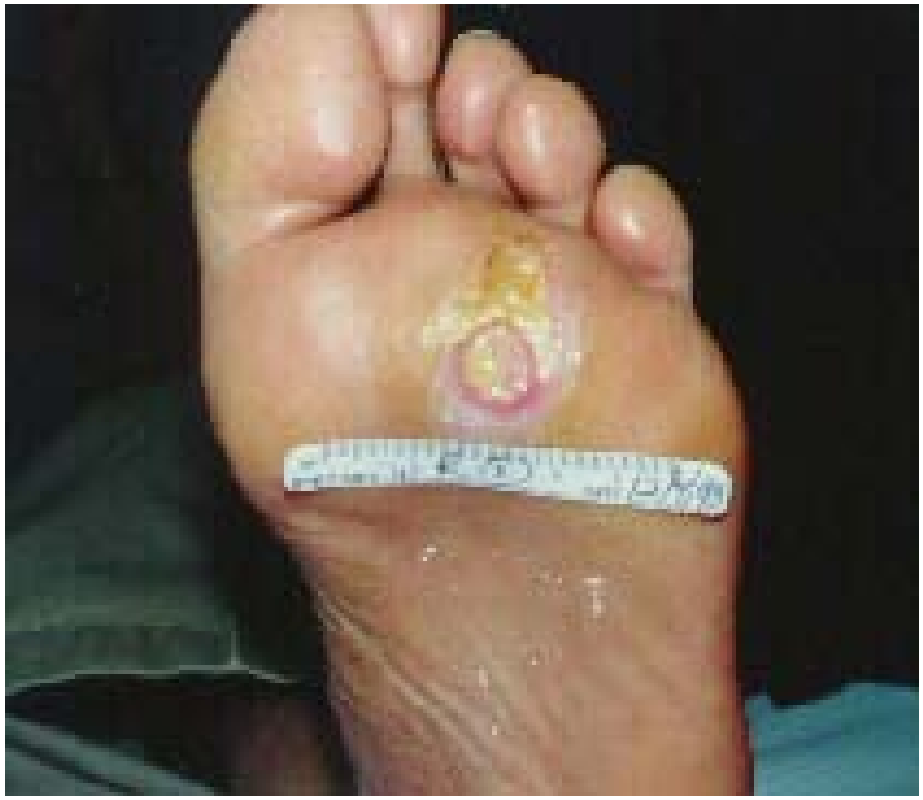
About 60 to 70 % of people diagnosed with diabetes develop nerve damage, known as diabetic neuropathy.

Neuropathy develops slowly and often times a person is unaware that they are loosing sensation in their extremities.



Monofilament applied to the planter surface of the foot to the point of buckling - failure of patient to sense this pressure indicates neuropathy

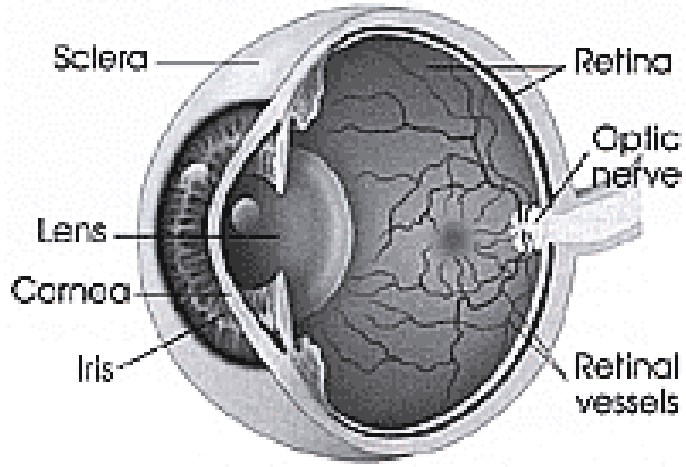


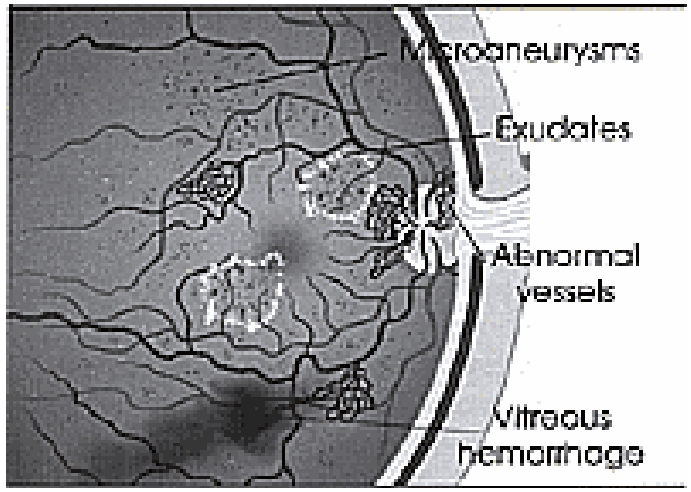


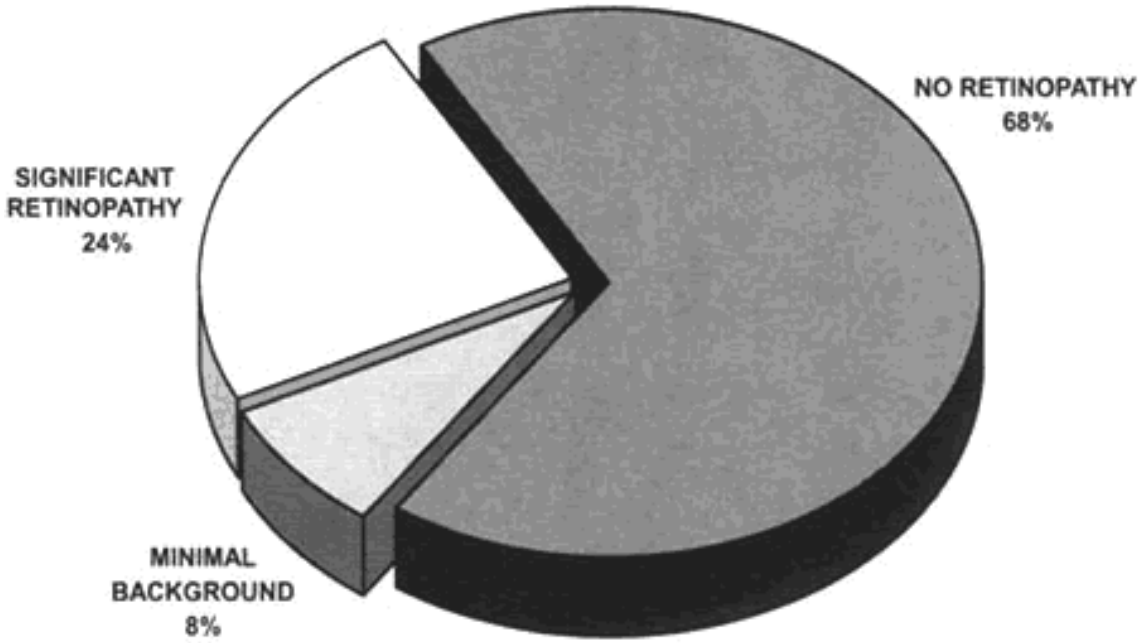
Non-healing ulcers
in patients with diabetes

Normal vision

Vision with diabetic retinopathy

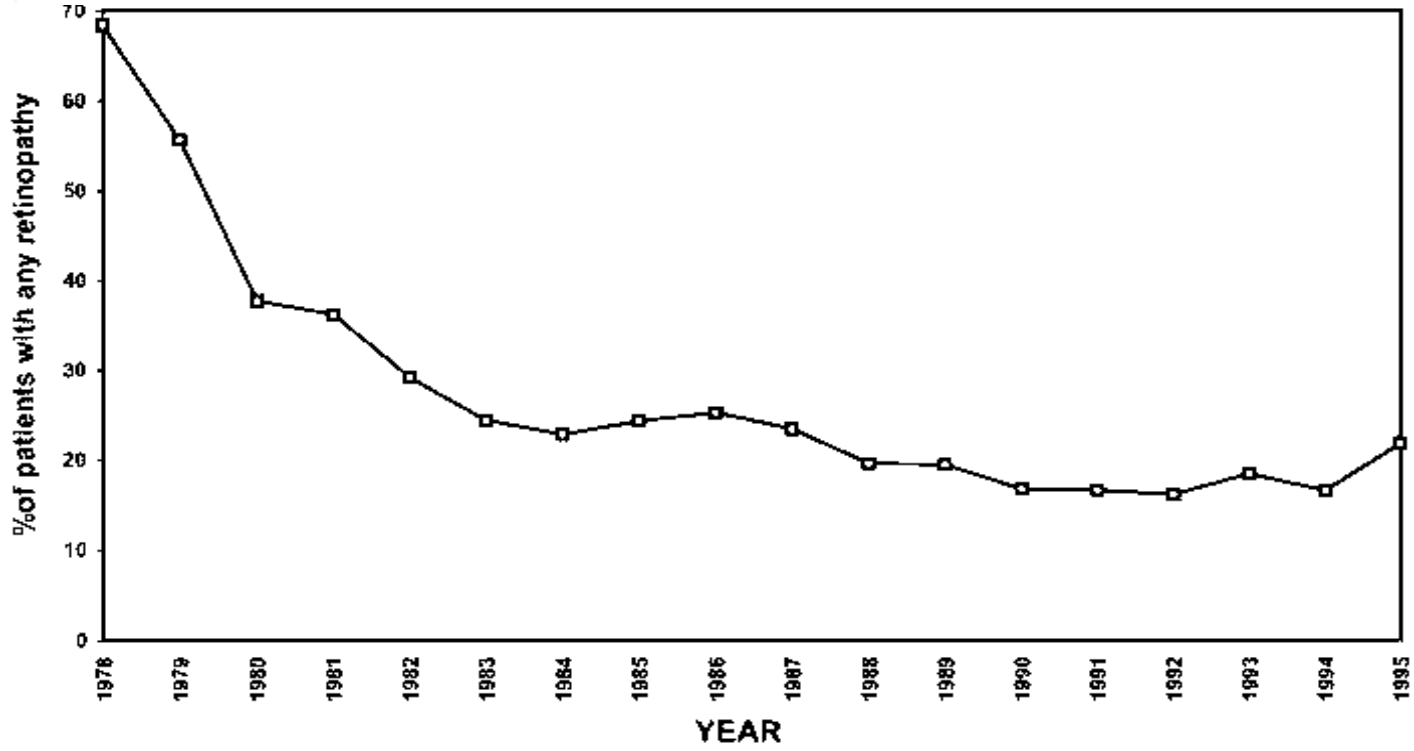


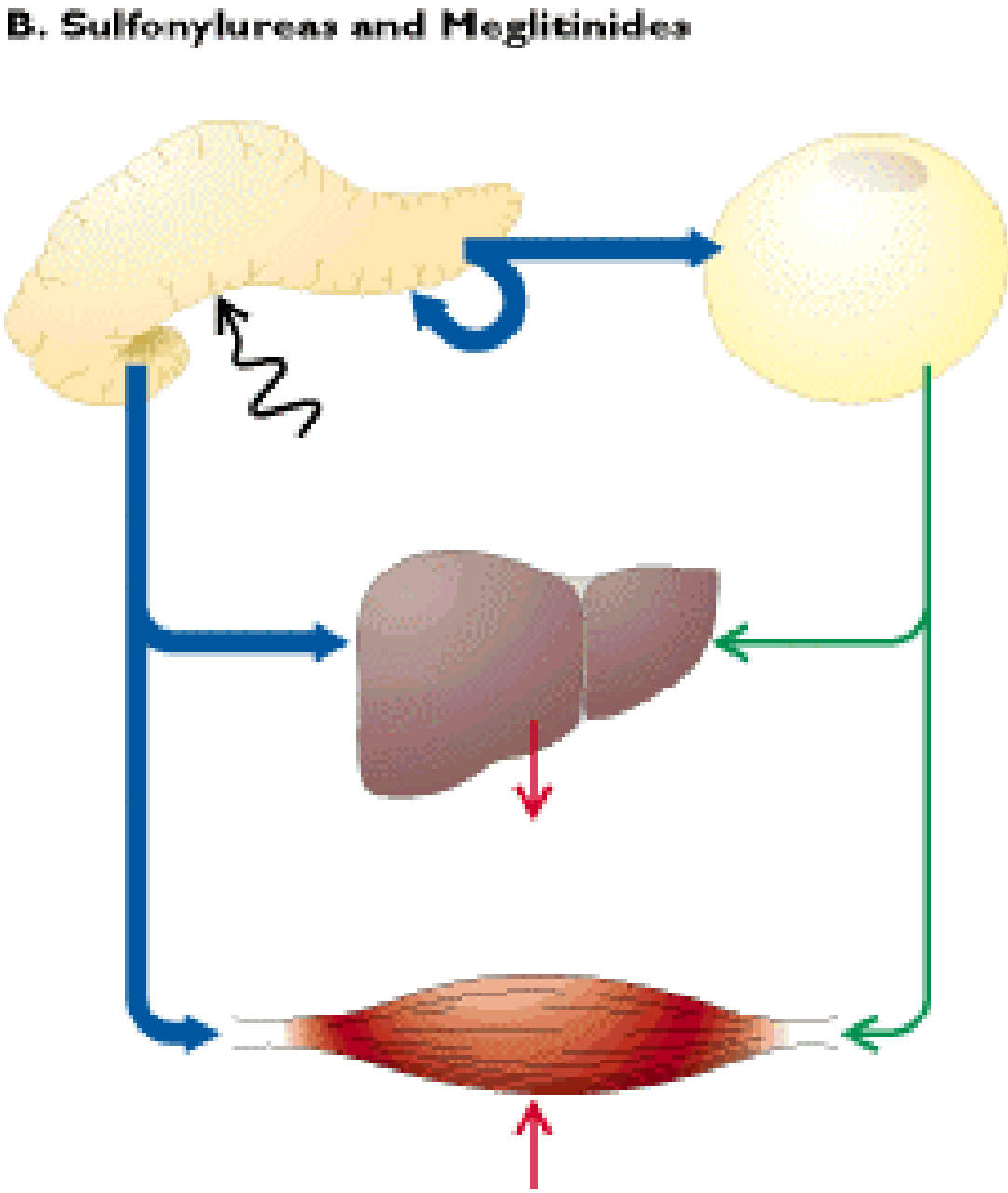




Prevalence of retinopathy in diabetic patients

Findings at first diagnosis





Sulfonyloureas

- Stimulate β cells to secrete more insulin

- First-line oral drugs. Most patients can take sulfonylureas for 7 - 10 years before they lose effectiveness.

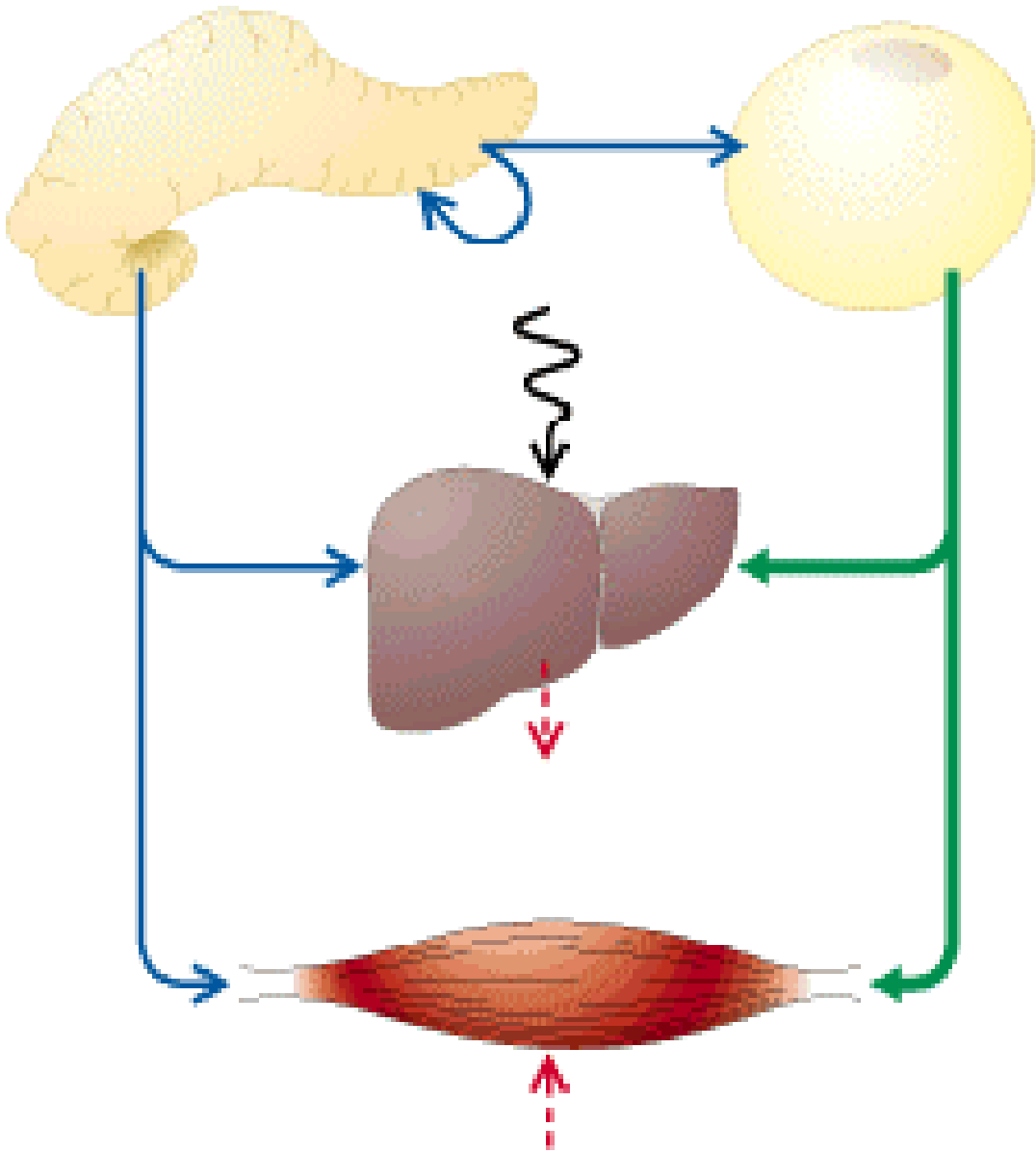
Side effects: **weight gain, water retention, hypoglycemia.**

Meglitinides

- Stimulate β cells to secrete more insulin
- Rapidly metabolized and short-acting. If taken before every meal, they actually mimic the normal effects of insulin after eating.

Side Effects. **Side effects include diarrhea and headache.**

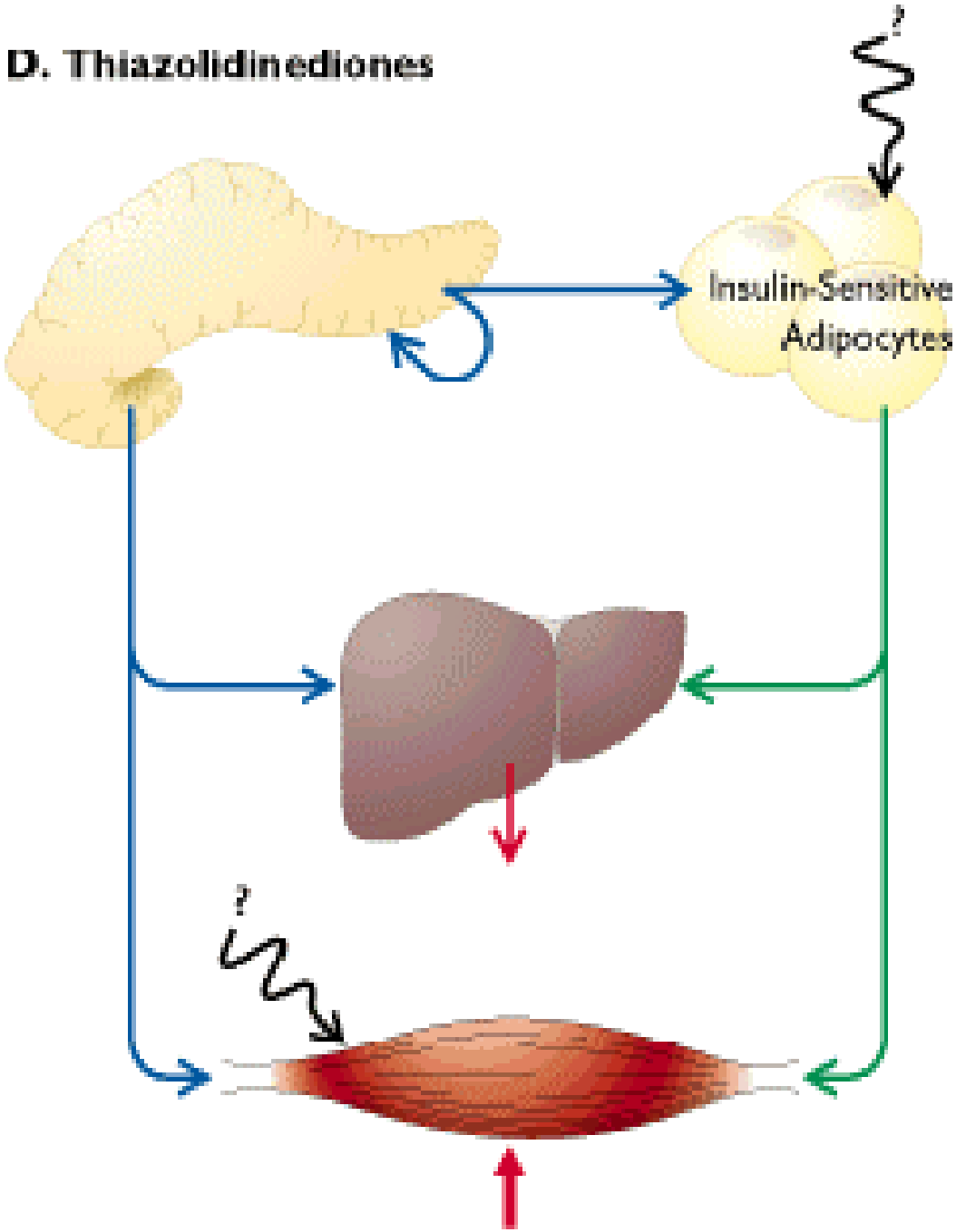
C. Metformin



Metformin

- Suppress hepatic glucose production and increases sensitivity of tissues to insulin
- No effect on insulin secretion
- A first choice medicine for most patients with type 2 diabetes who are insulin resistant, particularly if they are overweight.
- Does not cause hypoglycemia or add weight,

Side effects: A metallic taste, gastrointestinal problems, including nausea, and diarrhea



TZD (PPARγ agonists)

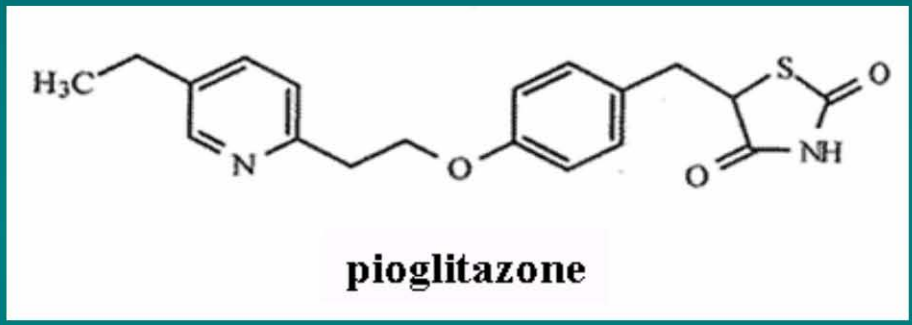
- Promote peripheral glucose utilization
- No effect on insulin secretion
- Promote differentiation of smaller, insulin-sensitive adipocytes
- Usually taken once or twice per day in combination with other oral drugs or insulin; it may take several days before the patient notices any results from them and several weeks before they take full effect.

Side Effects: Increase fluid build-up, which can cause or worsen heart failure in some patients, increased risk for heart attack, significant weight gain, increased risks for bone fracture, hepatotoxicity.

Thiazolidinediones (TZD): pharmacological activators of PPARγ

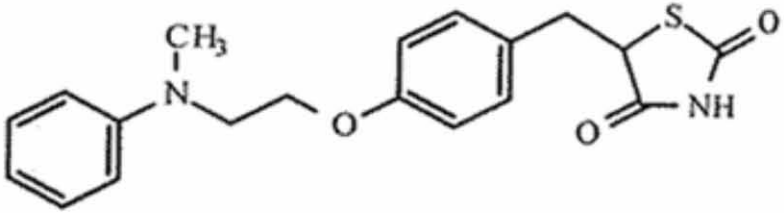
In clinical use

ciglitazone



pioglitazone

troglitazone



rosiglitazone

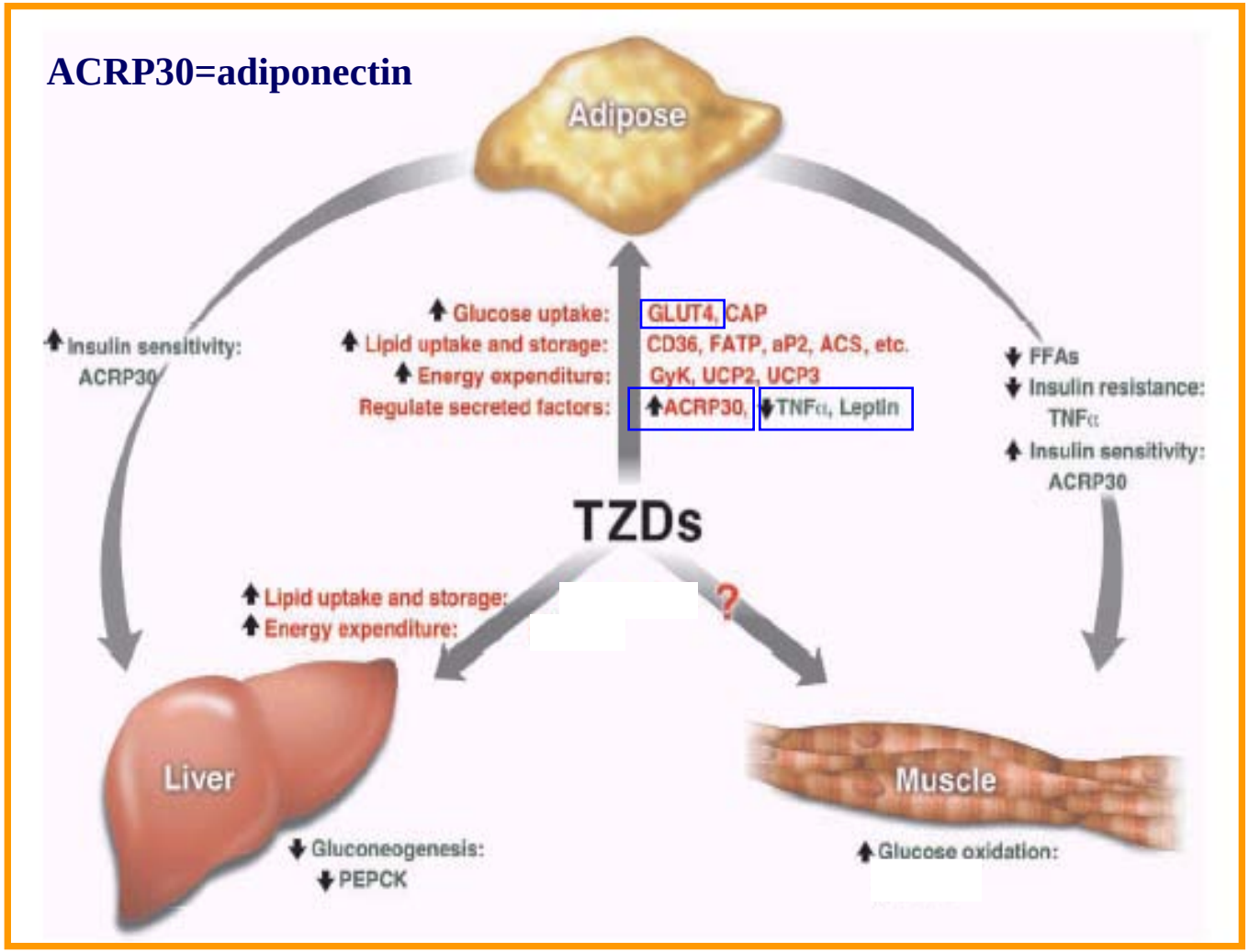
TZDs as drugs

- **The thiazolidinediones are oral anti-diabetic drugs which were developed during the 1990s: troglitazone (first prescribed with warning, then withdrown), rosiglitazone, pioglitazone.**

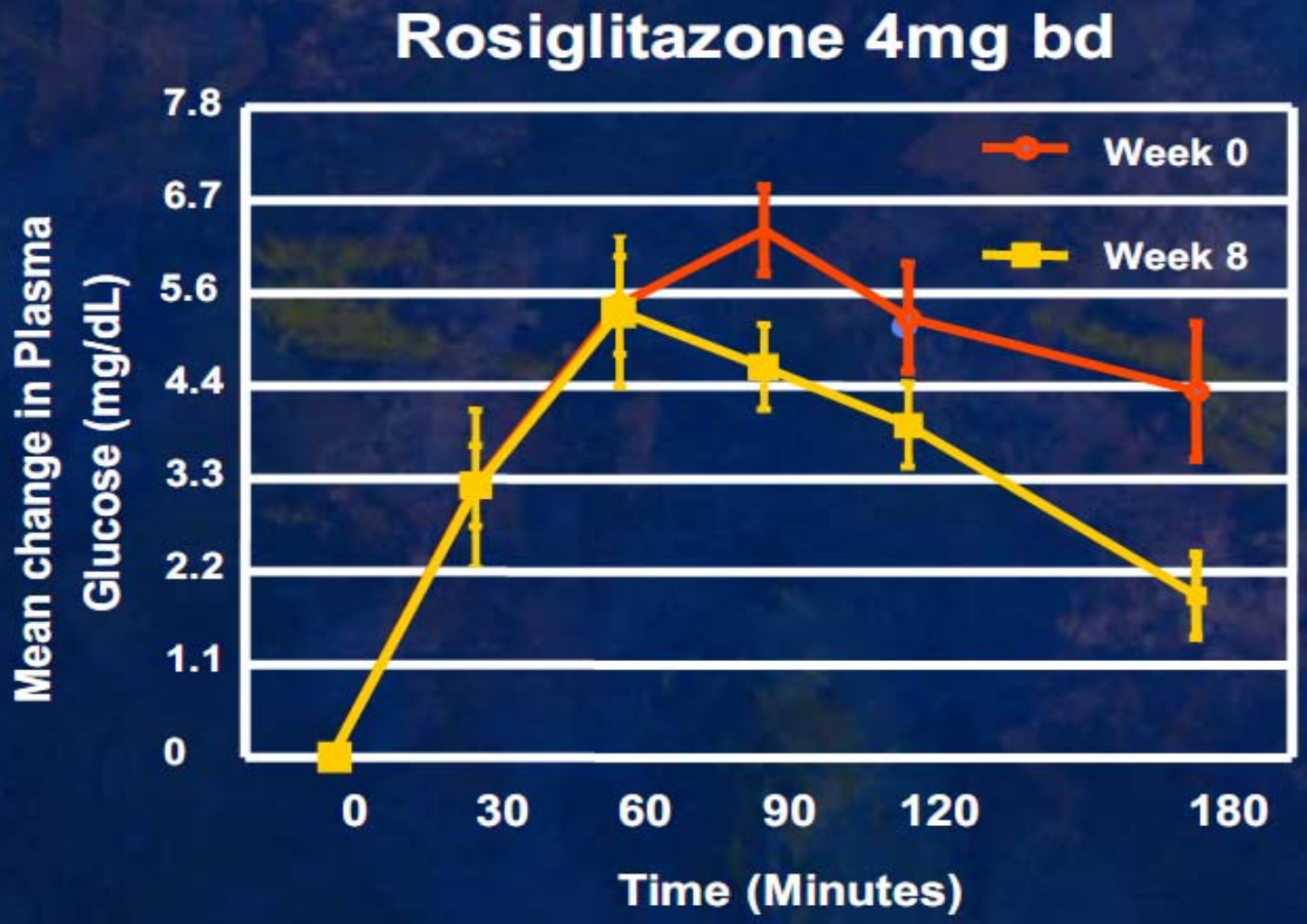
- **Discovered in Japan.**

- **Used mostly in USA and Japan (but also in EU) both as mono-therapy and in combination with other drugs.**

- **Value of the market in USA:**
- *** 8 billion $ in 2003,**
- *** 20 billion $ in 2006.**



Effects of rosiglitazone on Post-Prandial Glycemia



TZD – effect of insulin resistance

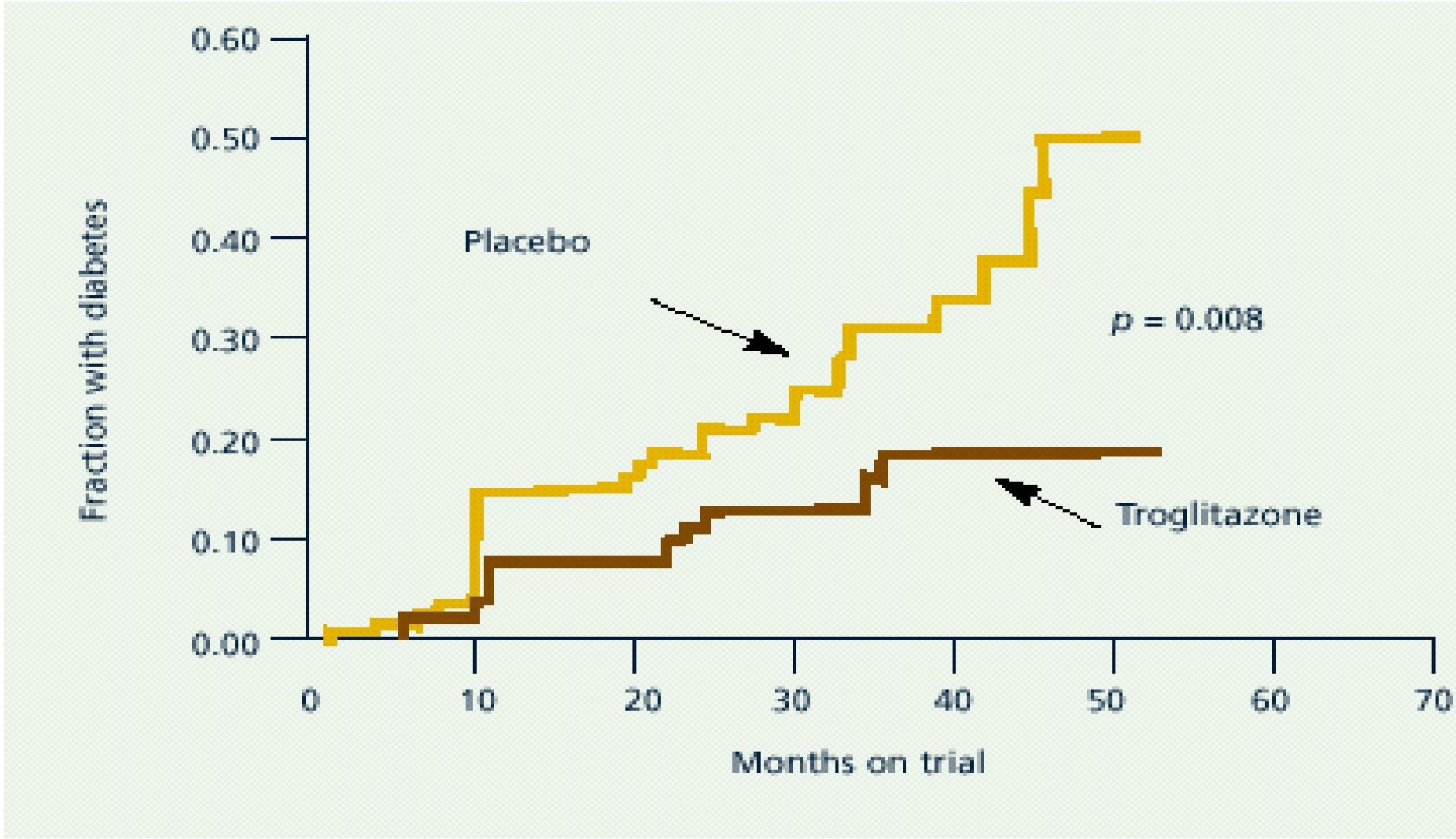
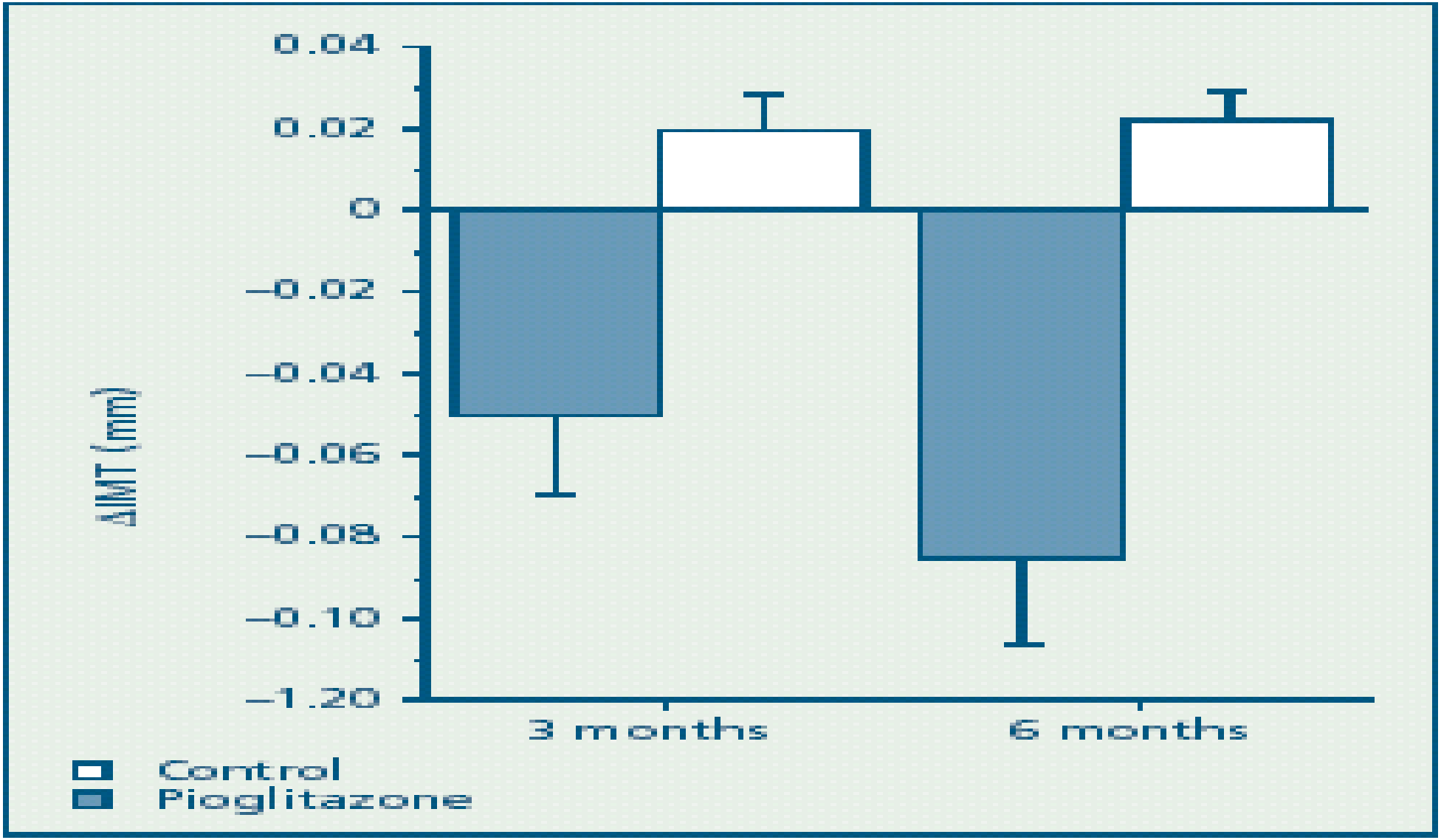
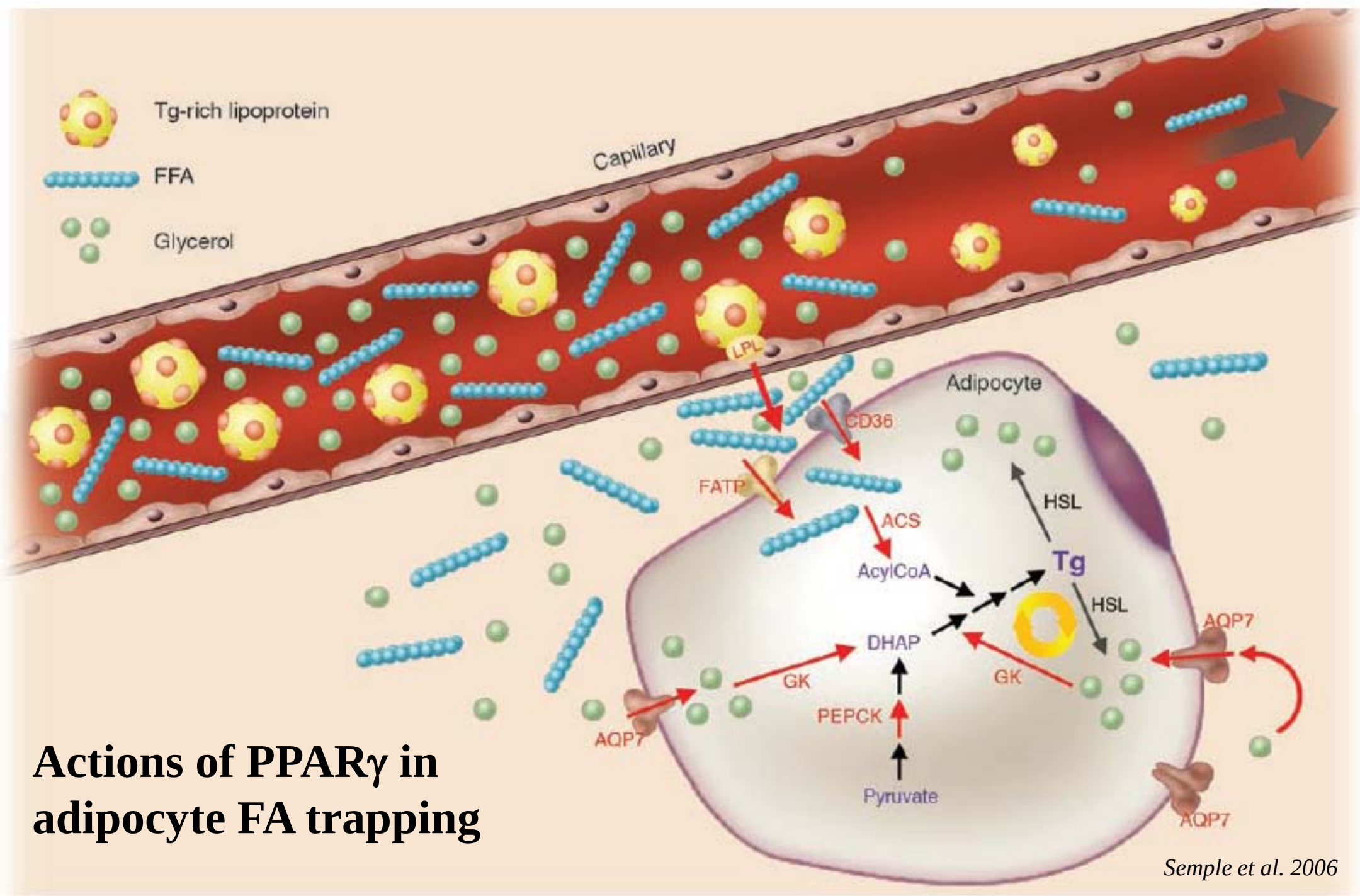


Figure 2: Cumulative incidence rates of diabetes development.

TZD – effect on neointima formation

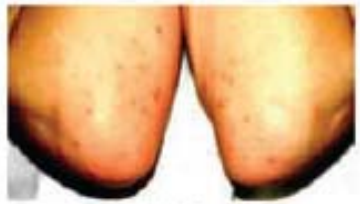




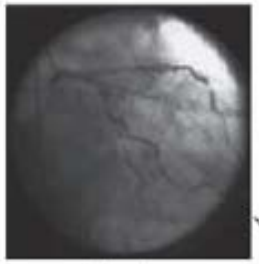
Actions of PPARγ in adipocyte FA trapping

Semple et al. 2006

PPARγ ligand resistance syndrome (PLRS)

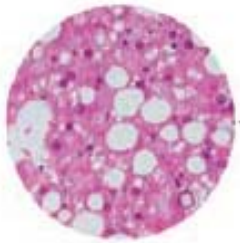


Dyslipidemia

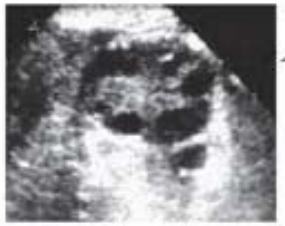


Early atherosclerosis

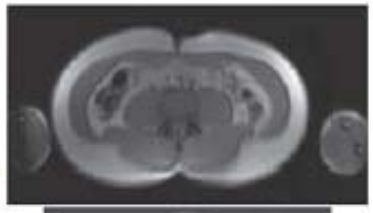
Early hypertension

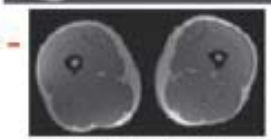


Hepatic steatosis



Polycystic ovaries

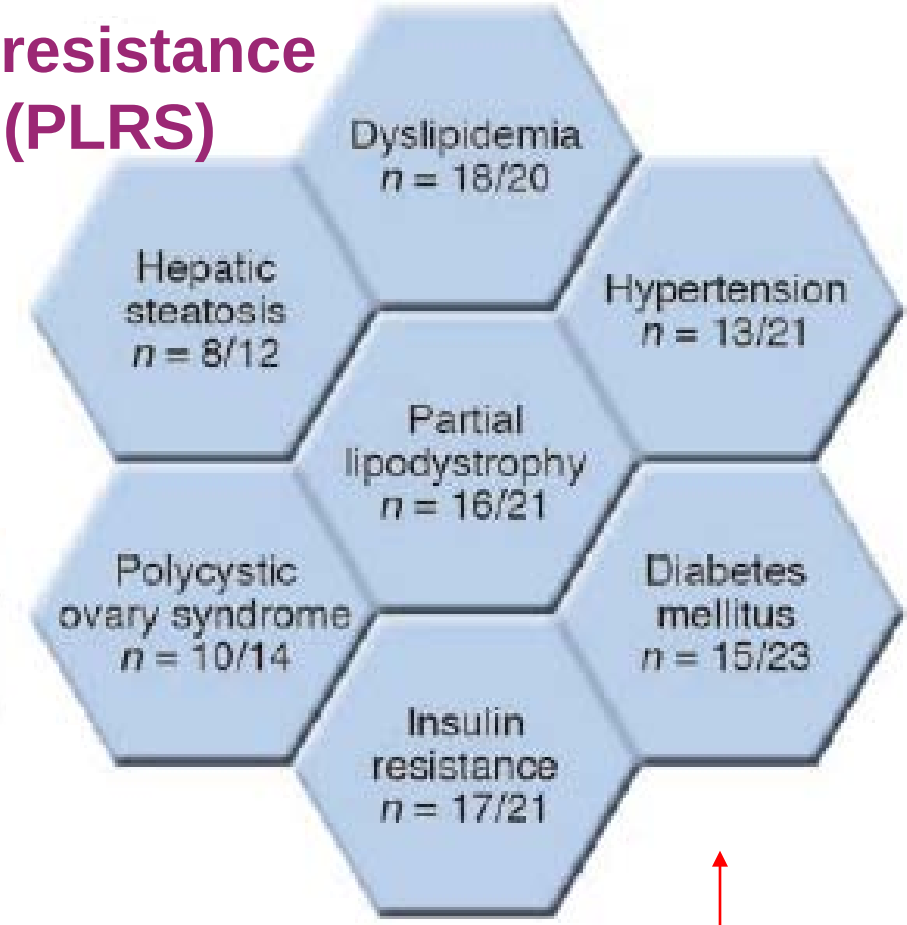




Limb/gluteal lipodystrophy

Severe insulin resistance

Semple et al. 2006



Phenotypic characteristics of PLRS subjects. The denominator of *n* refers to the number of subjects for whom information is available.

A 41-year-old woman with a heterozygous C131Y PPARg mutation

Figure 2. Insulin-triggered pathways in cells such as myocytes and hepatocytes may incorporate the molecular events that set the high insulin resistance of type 2 diabetes. In insulin-responsive cells, insulin binds to the a subunit of the insulin receptor, causing the b subunit to phosphorylate both itself and a cytoplasmic protein, insulin receptor substrate 1 (IRS-1). In turn, IRS-1 interacts with proteins incorporating an SH2 domain. Among more than 20 such proteins identified, PI-3-kinase is depicted. Through interactions with additional proteins, it enables the glucose transporter GLUT4 to become active at the cell surface. Other molecules transmit the signal to activate glycogen synthase, the rate-limiting enzyme in glycogen production. Still others serve to activate transcription factors, DNA-binding proteins that regulate genes. Although the most obvious molecular explanation for insulin resistance would be mutation in the insulin receptor, less than 1% of patients with type 2 diabetes exhibit such a flaw; instead, patients may have one or a series of defects limiting levels or function of many of the intermediate transduction molecules.

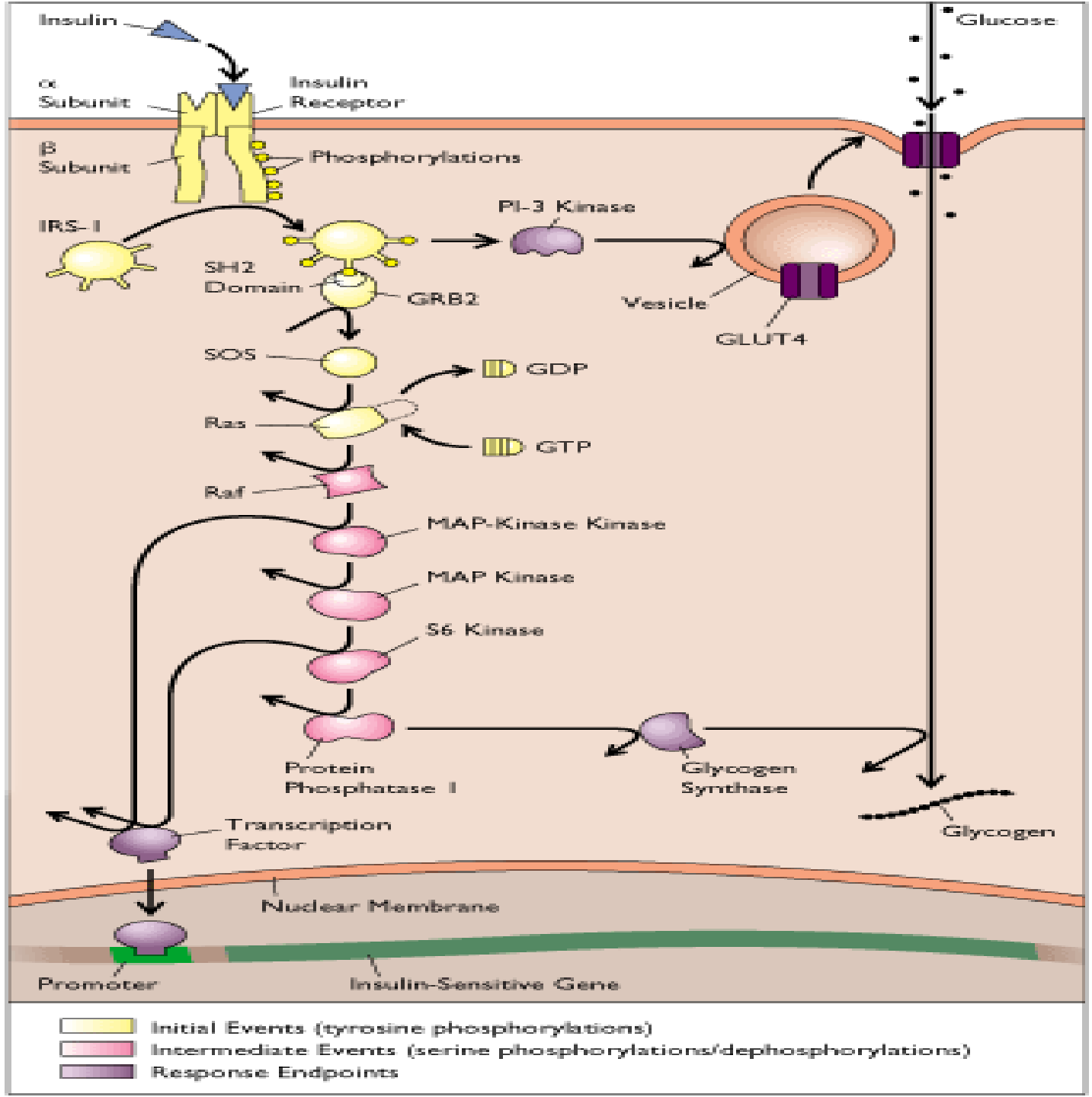


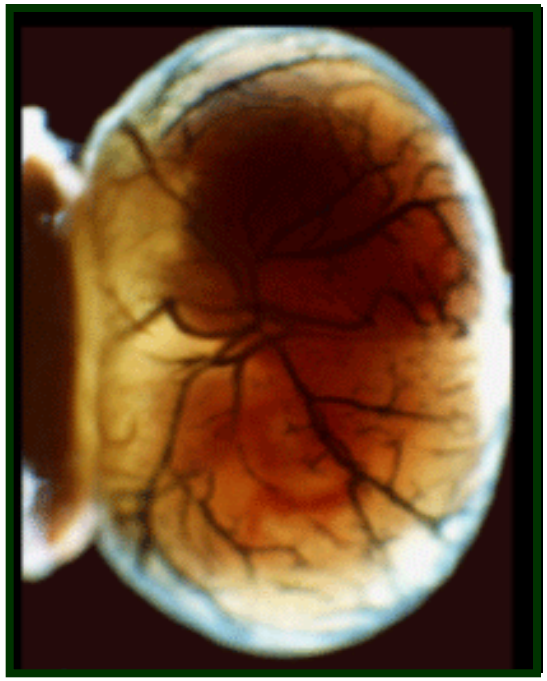
Illustration: Seward Hwng

PPARγ

↓ Inflammatory cytokine synthesis
Leukocyte adhesion
Blood pressure

PPARγ null mice are not viable, due to defective placental vascularization

PPARγ



PPARγ KO mice

Not viable

If rescued they show:
- lipodystrophy
- multiple intestitial hemorrhages

But:
- himeric or heterozygous PPARγ KO mice are protected (!) from insulin resistance, possibly due to the presence of smaller, insulin-sensitive adipocytes.

Thus:
PPARγ deficiency has the same protective effect as PPARγ activation. Well..... (?!)

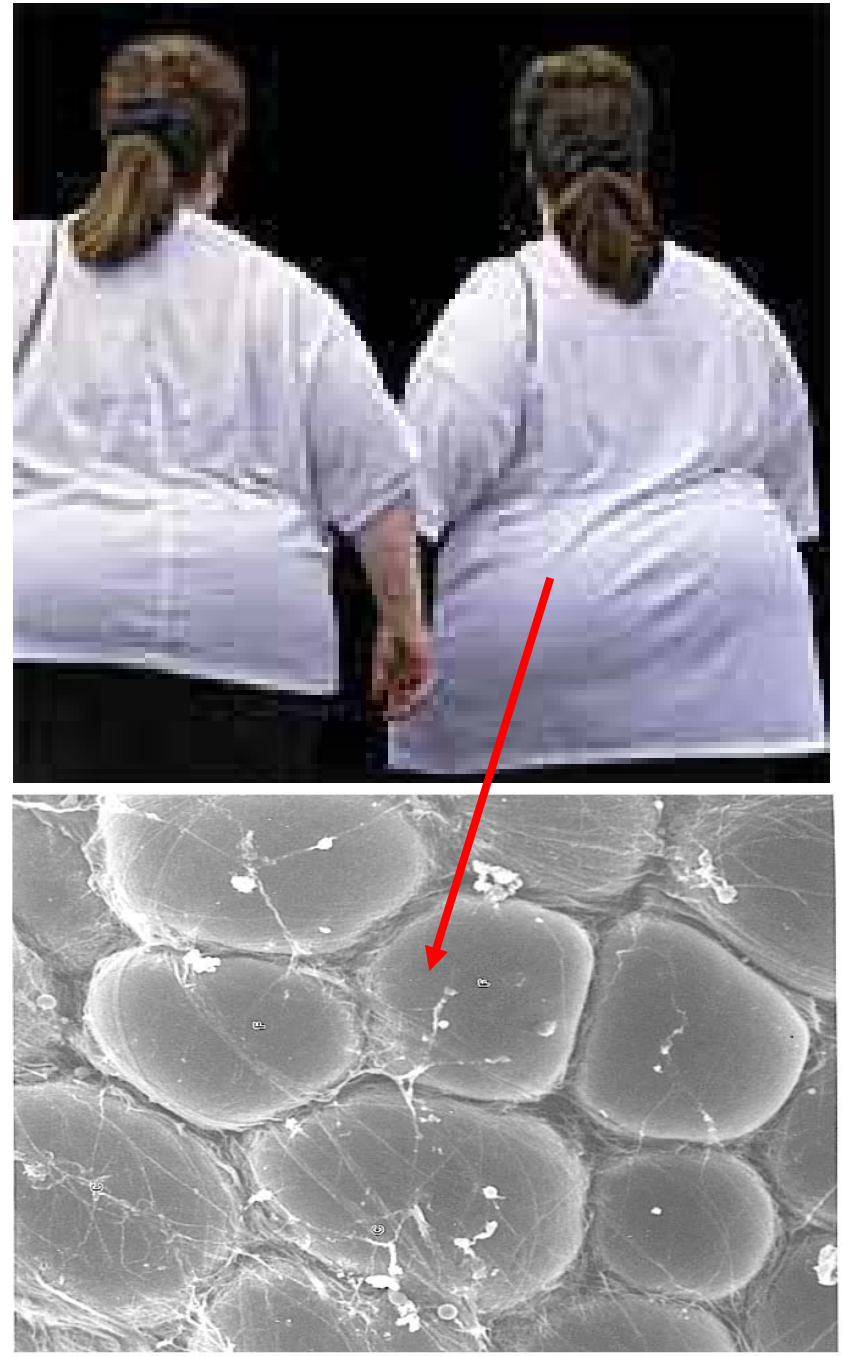
Adipose tissue as an endocrine organ

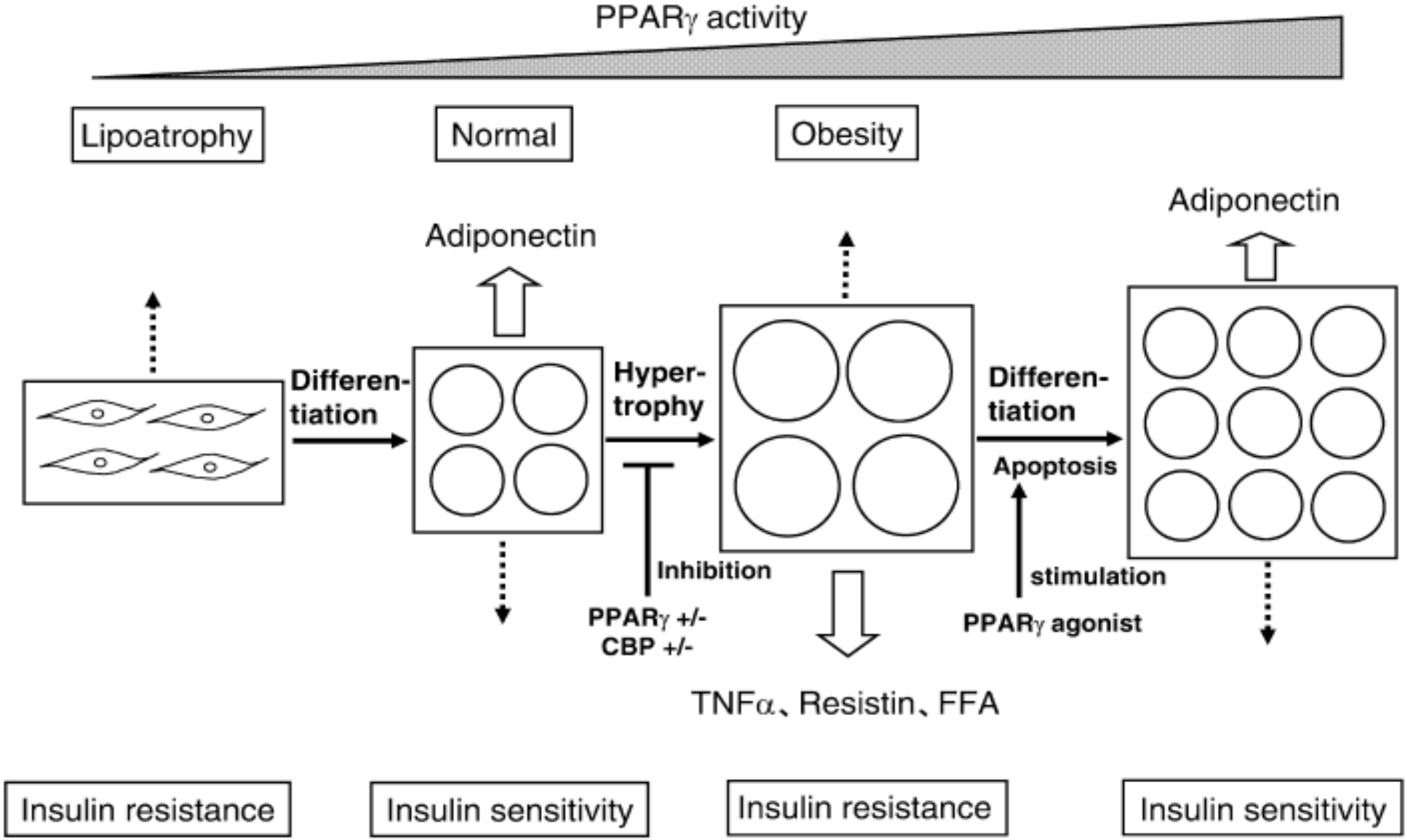
- Adipocytes secrete a number of important mediators, among others:

  * TNFα
  * interleukin-6
  * resistin
  * adiponectin
  * leptin

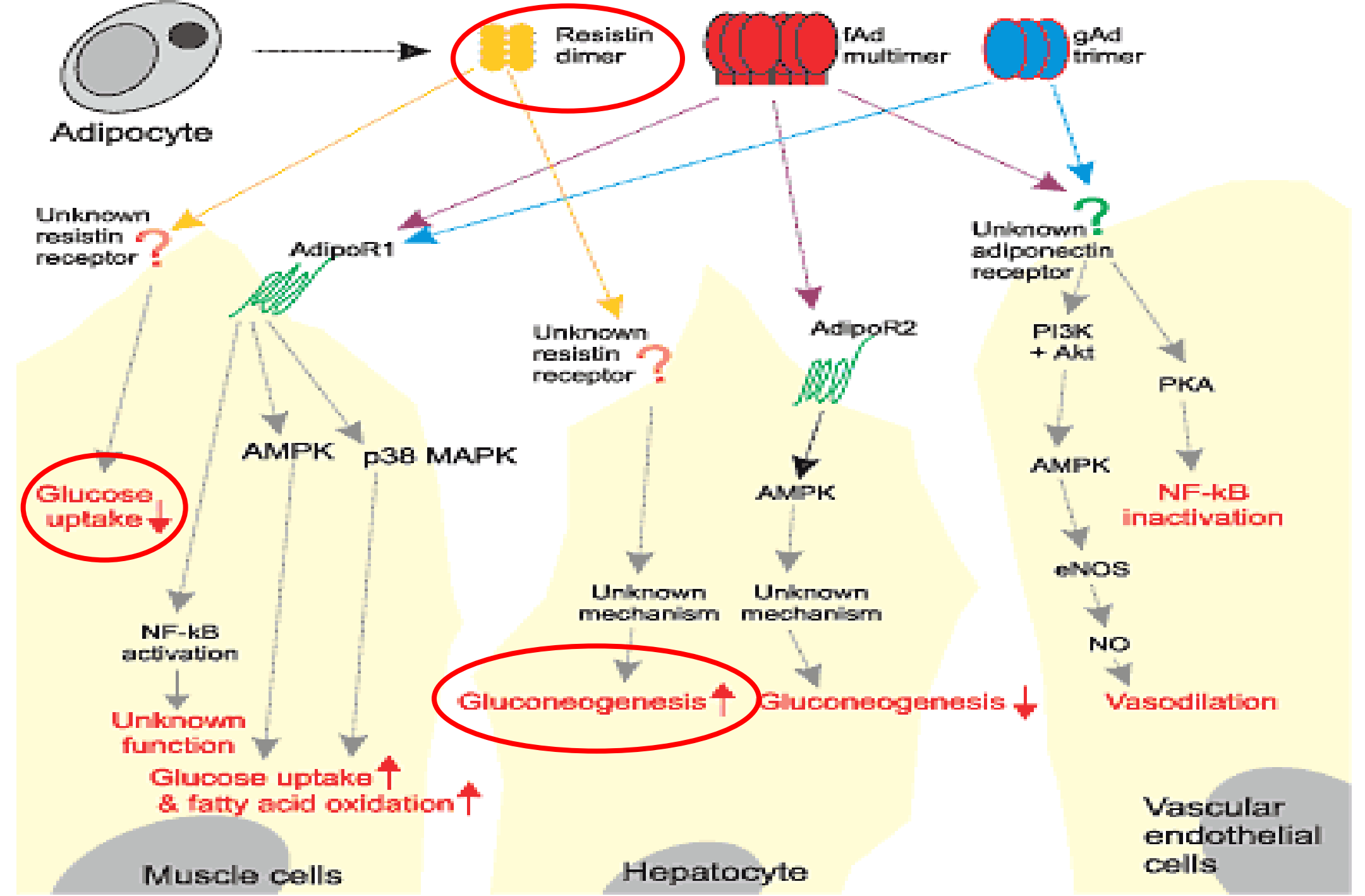
- Effect of TZD:

  * ↑ adiponectin
  * ↓ TNFα
  * ↓ IL-6
  * ↓ resistin
  * ↓ leptin





The mechanisms by which PPARγ regulates insulin sensitivity and anti-atherosclerosis.


Adipocyte
Resistin dimer
fAd multimer
gAd trimer
Unknown resistin receptor
AdipoR1
Unknown resistin receptor
AdipoR2
Unknown adiponectin receptor
PI3K + Akt
PKA
AMPK
p38 MAPK
AMPK
AMPK
NF-kB inactivation
Glucose uptake
eNOS
NF-kB activation
Unknown mechanism
Unknown mechanism
NO
Gluconeogenesis
Gluconeogenesis
Vasodilation
Unknown function
Glucose uptake & fatty acid oxidation
Muscle cells
Hepatocyte
Vascular endothelial cells

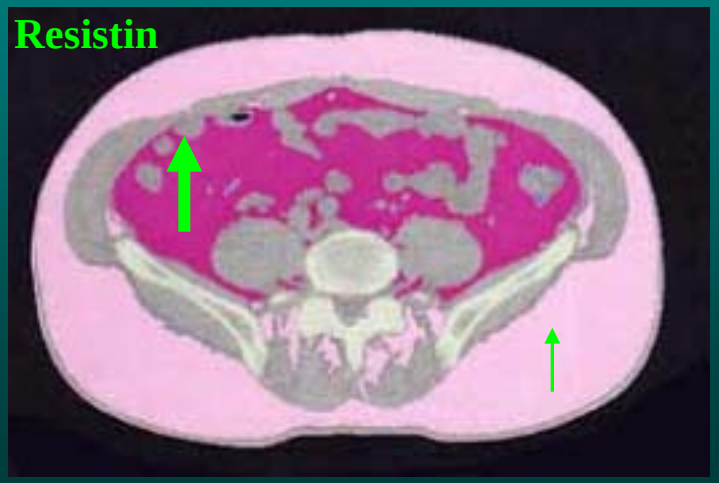
Resistin

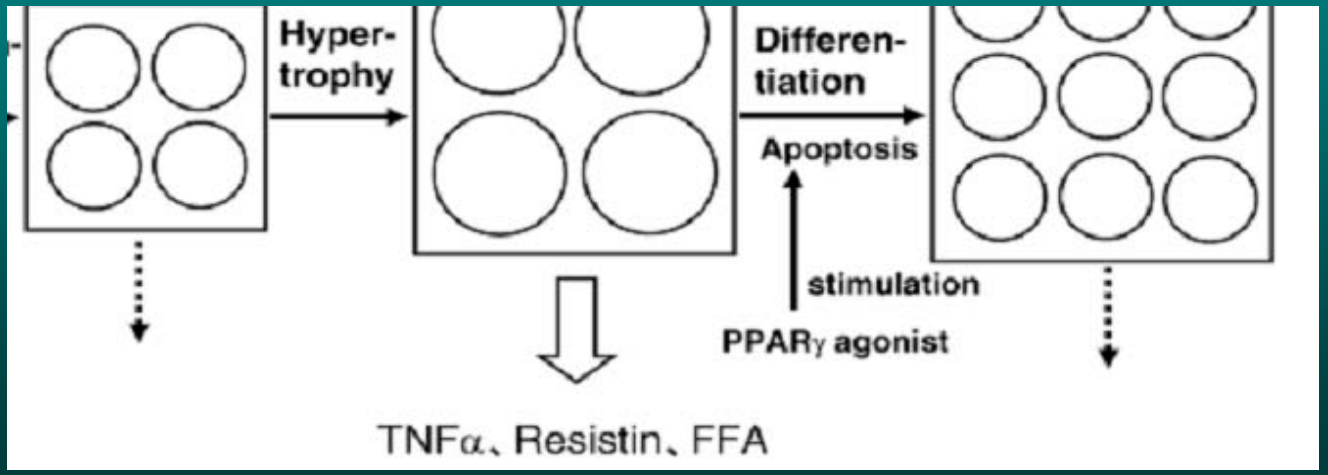
- Resistin is a secreted protein induced during adipocyte differentiation, circulating as a monodimer or dimer.

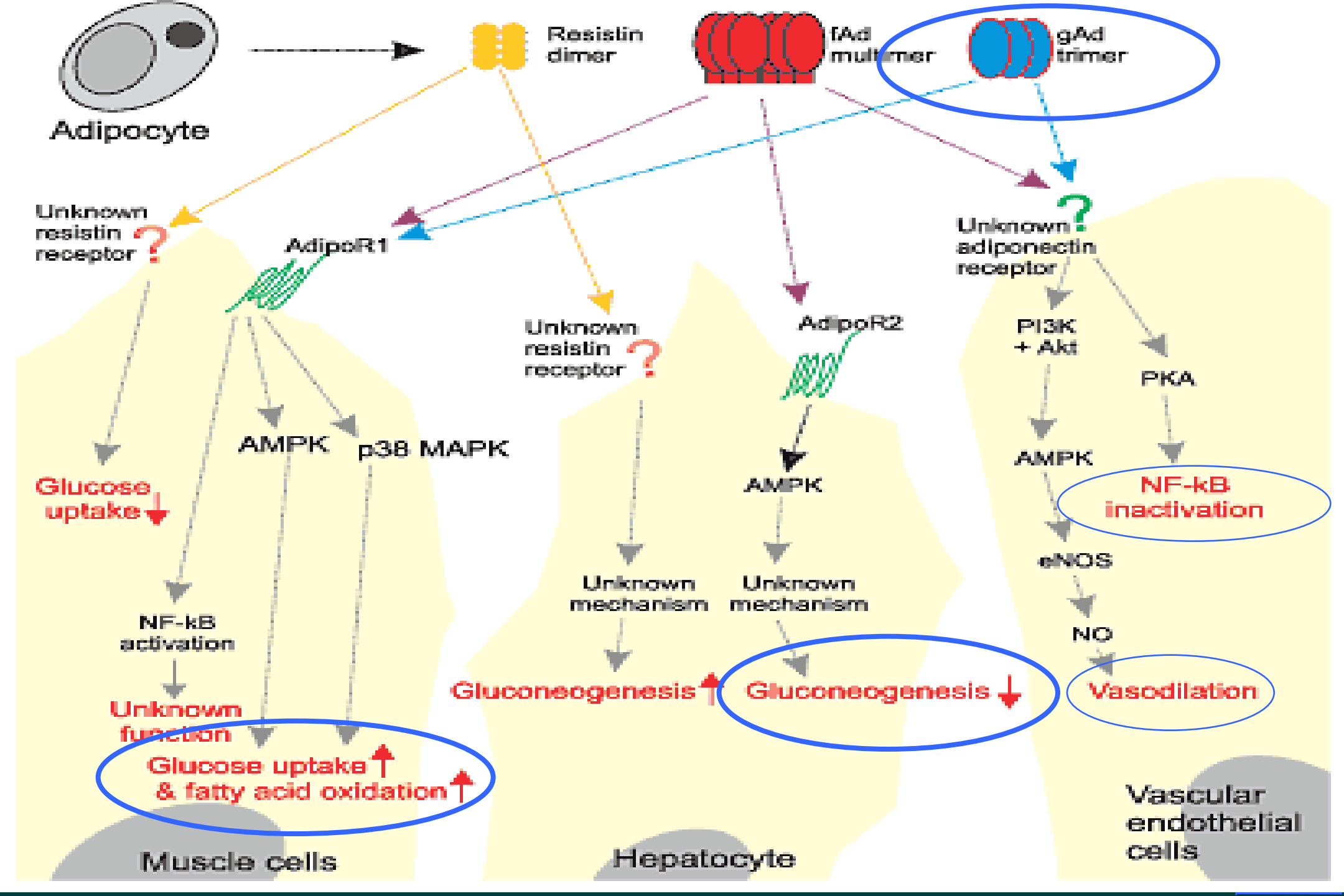
- Expressed mostly in white adipose tissue, detectable also in serum resistin expression in visceral fat is 15-fold higher than in subcutaneous fat. In human high expression is found in monocytes.

- TZDs decrease the expression of resistin.

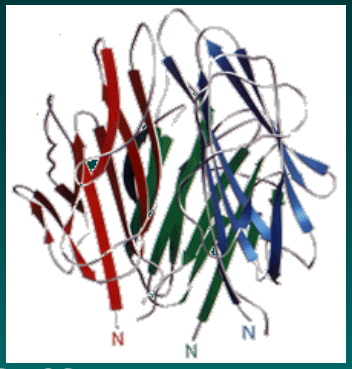
- The serum level of resistin is high in obese and insulin resistant patients, but decreases with dieting.



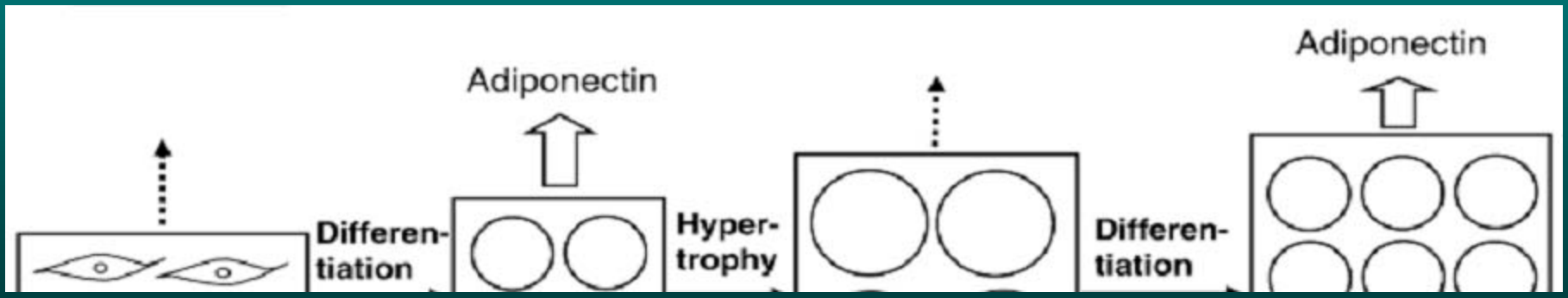



Adipocyte
Resistin dimer
fAd multimer
gAd trimer
Unknown resistin receptor
AdipoR1
Unknown resistin receptor
AdipoR2
Unknown adiponectin receptor
PI3K + Akt
PKA
AMPK
p38 MAPK
AMPK
AMPK
Glucose uptake
NF-kB inactivation
eNOS
NF-kB activation
Unknown mechanism
Unknown mechanism
NO
Unknown function
Gluconeogenesis
Gluconeogenesis
Vasodilation
Glucose uptake & fatty acid oxidation
Muscle cells
Hepatocyte
Vascular endothelial cells

Adiponectin



- Adiponectin levels decreases concomitantly with weight gain.
- Receptors for adiponectin are highly expressed in skeletal muscle and in hepatic tissues.
- Decreased adiponectin levels are associated with insulin resistance and hyperinsulinemia.
- Patients with type-2 diabetes are reported to exhibit decreased circulating adiponectin.
- High adiponectin levels are associated with a reduced risk of type-2 diabetes.
- Thiazolidinediones elevate adiponectin in insulin-resistant patients.



PPARγ paradoxes:

- Low expression of PPARγ in the skeletal muscle (the major target tissue for insulin sensitizing)

** action is indirect, related with decreased level of free fatty acids and reduced expression of some adipocyte-derived factors (mostly TNF α)and increased production of adiponectin.*

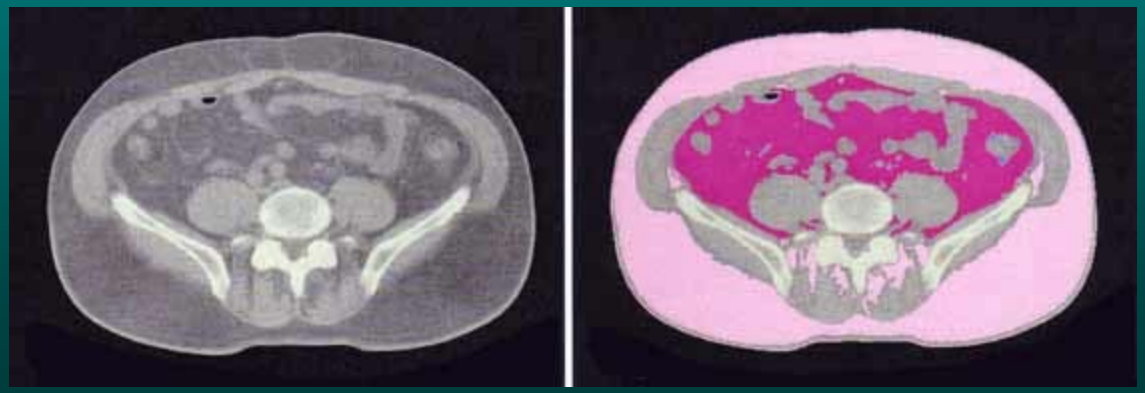
- PPARγ ligands cause weight gain (whereas obesity is the major cause of insulin resistance)

** only in subcatenous not in visceral fat – visceral fat is less sensitive to insulin*

- PPARγ deficiency (e.g. in PPARγ$^{+/-}$ mice) protects mice from insulin resistance (the same does PPARγ activation)

** such mice gained significantly less weight compared with wild-type mice*

** mice had higher core body temperature – greater rate of energy expenditure*



visceral fat (dark pink) and subcutaneous fat (light pink).

MODY - Maturity-Onset Diabetes of the Young

Main characteristics:

- Diabetes presents at a young age, usually less than 25 years of age. Typical patients are not necessarily overweight. It affects 1-2% diabetic people, and may often go unrecognised in its early stages.

- MODY runs in families through several generations. A parent with MODY has a 50% chance of passing on MODY to their child, because of autosomal dominant inheritance.

- People with MODY do not always need insulin treatment and can often be treated with diabetes pills or meal planning alone.

- People with MODY do not produce enough insulin.

MODY was first described by in 1974 in a group of young people with diabetes who were treated without insulin 2 years or more after diagnosis. The first MODY gene was found in 1992, and there are now six known genes in which defects will cause MODY.

The classifications of MODY

Type 1: Affected gene - HNF4α, uncommon; Defects in the HNF-4α also affect fatty acid synthesis in the liver.

Type 2: Affected gene - GCK (glucokinase), common; very mild and often symptomless, rarely causes any complications. Can often be treated with meal planning alone. Homozygotes: permanent neonatal diabetes.

Type 3: Affected gene - HNF1α, most common (25-75% of MODY); a progressive type; the gene defect causes a decrease in the kidneys re-absorption of glucose which results in glycosuria; patients may get diabetes complications. Usually diagnosed after puberty.

Type 4: Affected gene - IPF1 (insulin promotor factor 1), uncommon; relatively mild form of diabetes. Homozygotes: permanent neonatal diabetes.

Type 5: Affected gene - HNF1β, uncommon; defects in the HNF-1 can cause renal cysts and other abnormalities in kidney development. Kidney disease is often diagnosed before diabetes.

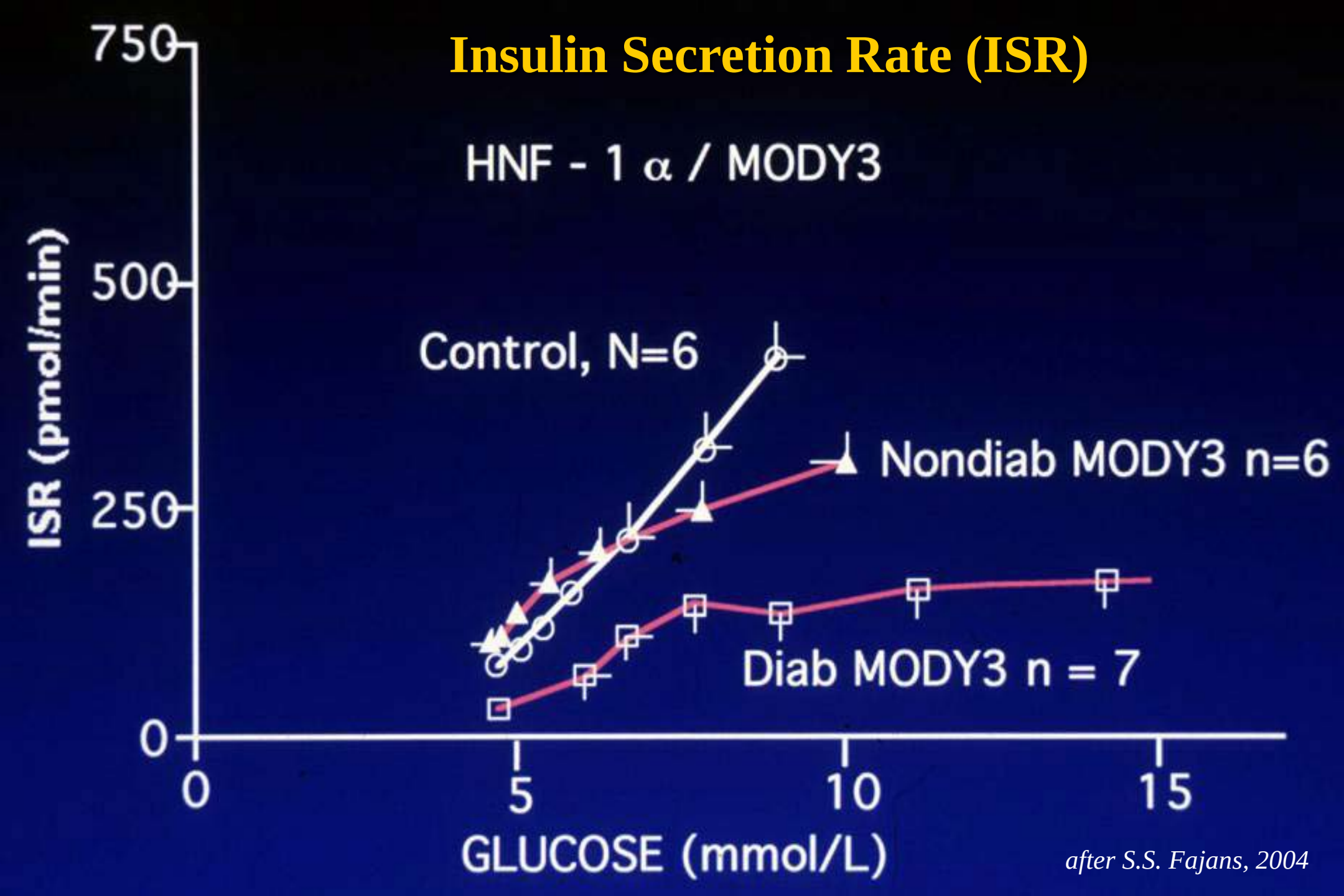
Type 6: Affected gene - Neuro D1 (neurogenic differentiation factor 1), very rare.

Distinguishing Clinical Characteristics of MODY and Type 2 Diabetes (DM2)

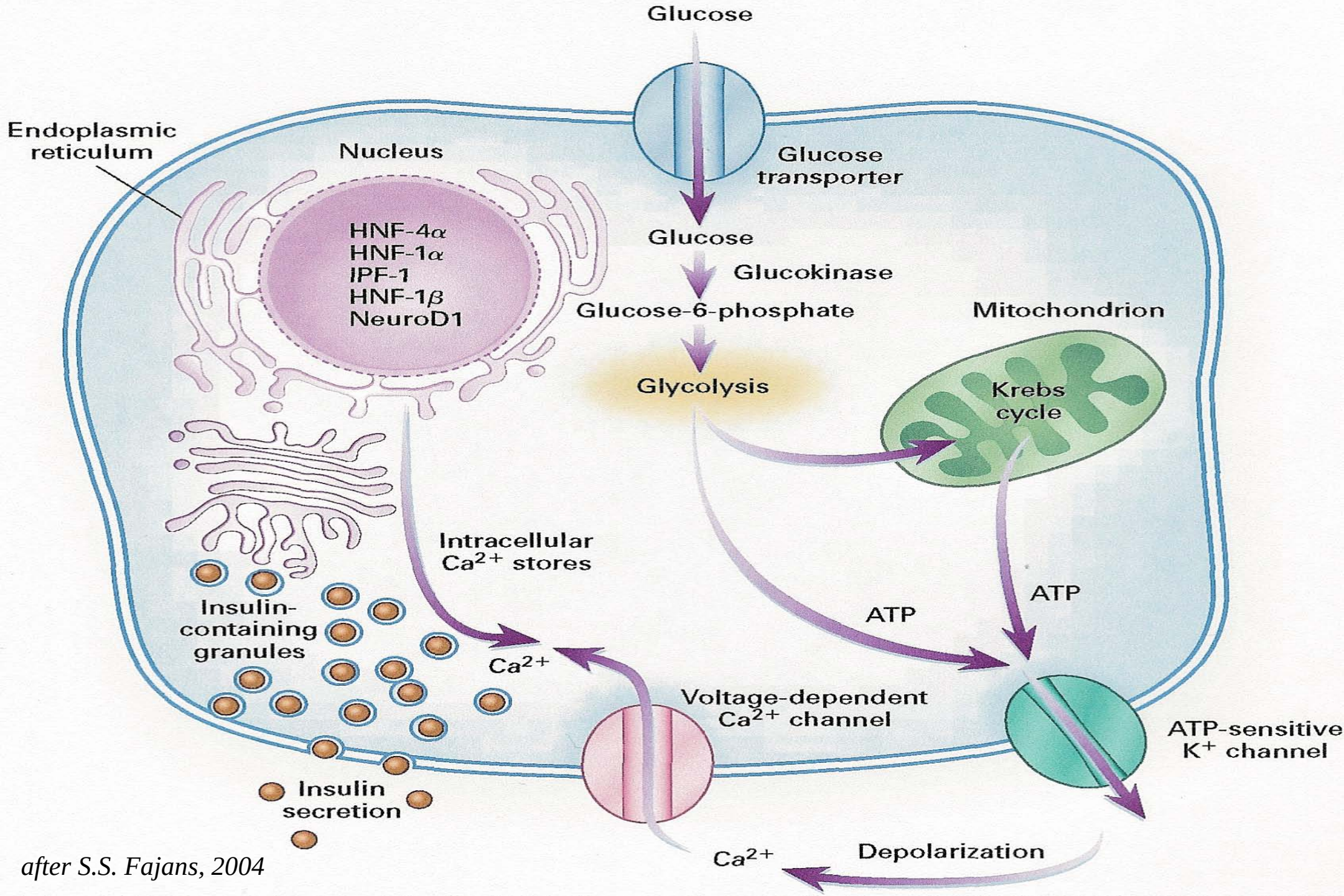
- **Mode of inheritance**
  - **MODY: Monogenic, autosomal dominant**
  - **DM2: Polygenic**
- **Age of onset**
  - **MODY: Childhood, adolescence, usually <25 years**
  - **DM2: Usually 40-60 years; occasionally in obese adolescents**
- **Pedigree**
  - **MODY: Multi-generational**
  - **DM2: Rarely multi-generational**

after S.S. Fajans, 2004

Insulin Secretion Rate (ISR)



after S.S. Fajans, 2004

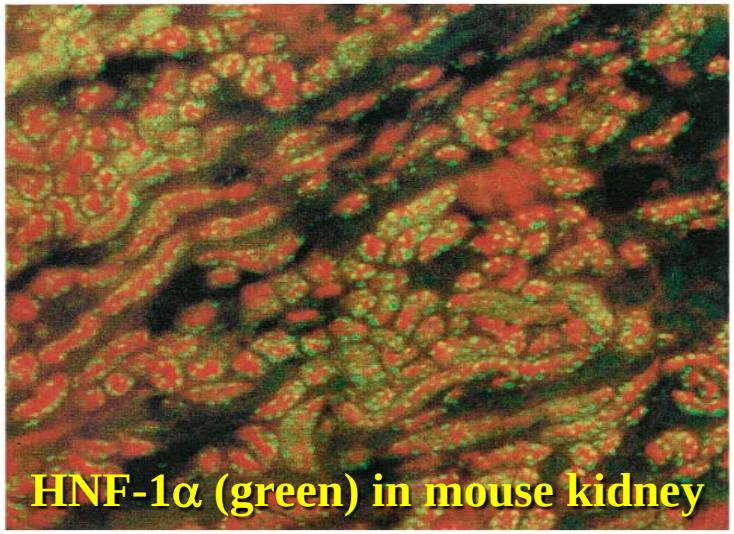


after S.S. Fajans, 2004

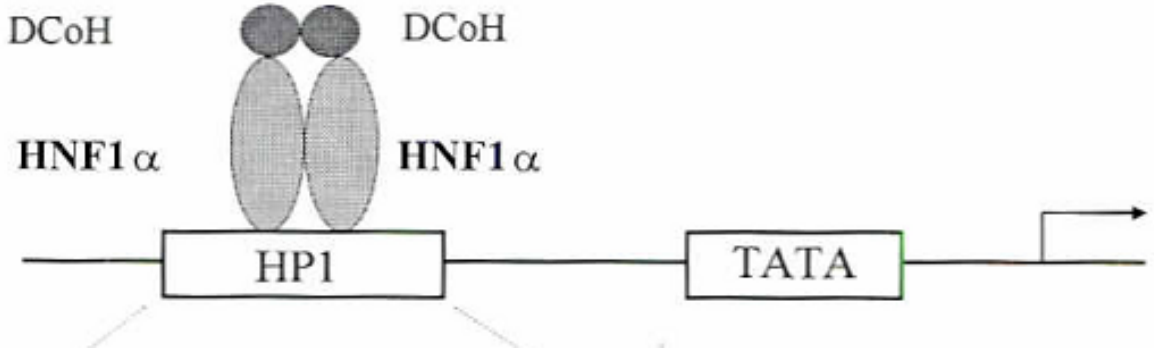
HNF-1α (hepatocyte nuclear factor-1α)

Hepatocyte nuclear factor 1 (HNF1) is involved in the regulation of a large set of hepatic genes, including albumin, β-fibrinogen, and α1-antitrypsin. It is a major regulator of glucose homeostasis, regulating the expression of genes that are expressed in the liver, kidney, and pancreas. Still orphan.

Regulate expression of the insulin gene, and genes of proteins involved in glucose transport and metabolism, and mitochondrial metabolism.



HNF-1α (green) in mouse kidney

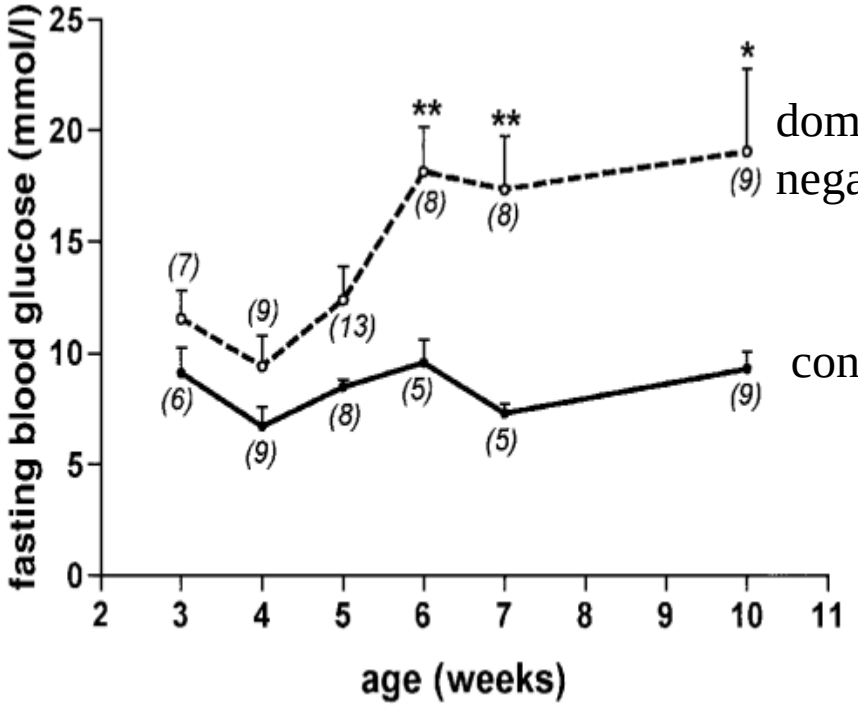


HNFα act as a homodimer or as a HNFα/HNFβ heterodimer

HNF-1α

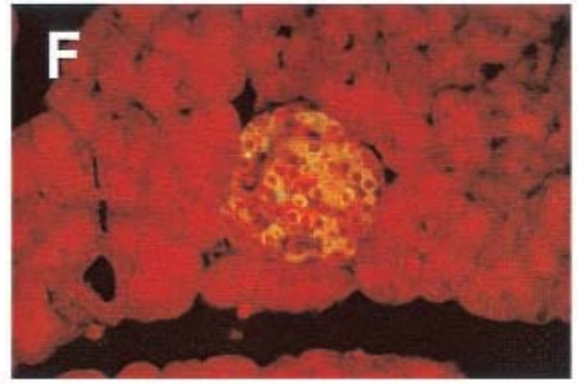
Mice lacking HNF1α exhibit hepatic, pancreatic, and renal dysfunctions. Renal proximal tubular reabsorption of glucose, phosphate, arginine, and other metabolites is affected, producing severe renal glucosuria, phosphaturia, and amino aciduria.

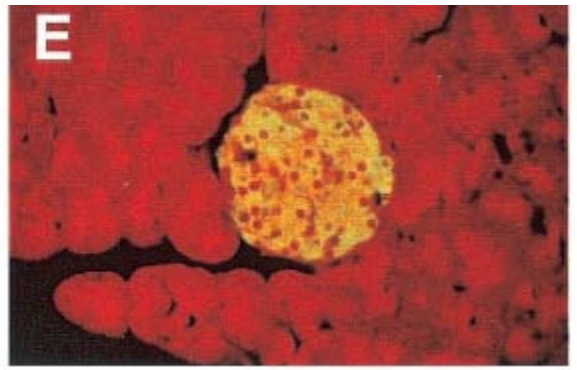
Homozygous mutant mice also exhibit a dramatic insulin secretion defect, which resembles that exhibited by patients with MODY-3, who carry mutations in the human HNF1 gene in the heterozygous state.



dominant negative HNF-1α

control





insulin staining

HNF-4α (hepatocyte nuclear factor-4α)

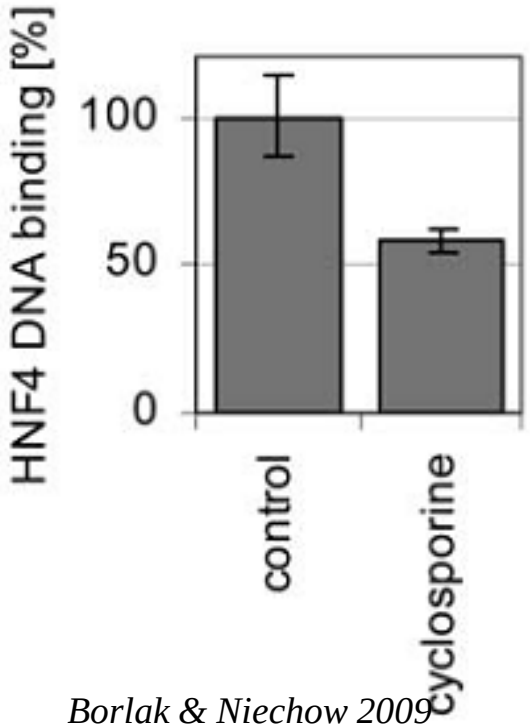
Recently adopted. Ligands: long-chain fatty acids and fibrates (ligands for PPARα!)

May use two promoters and generate several splicing forms. Act as a homodimer.

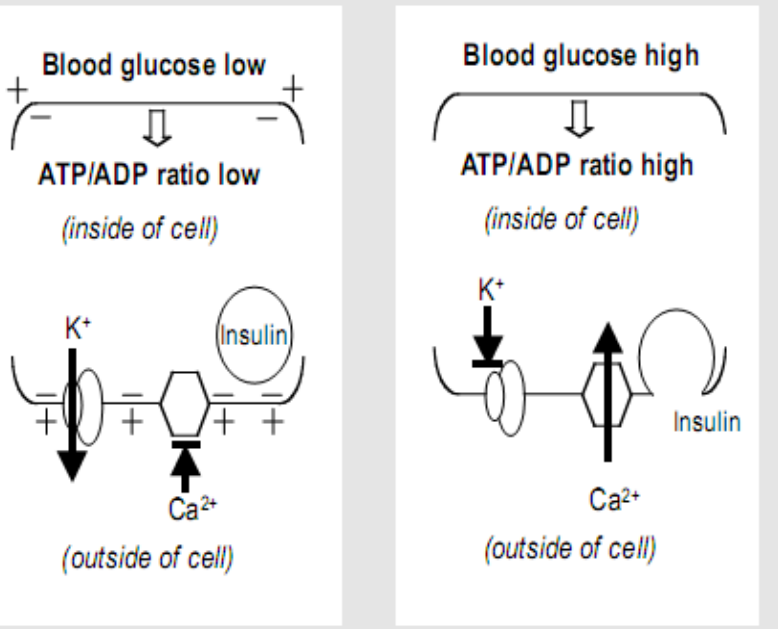
Regulate expression of genes involved in glucose transport and metabolism, and mitochondrial metabolism. It is essential in controlling transcription of many genes involved in lipoprotein metabolism in the liver. Its misfunction may contribute to DM 2.

Activity of HNF4α and HNF1α/β is mutually regulated. Promoter-2 of HNF4 contains HNF-1 response elements.

In prediabetic and diabetic MODY1 subjects, HNF-4α mutation leads to hepatocyte secretory defects in lipoproteins, resulting in decreased serum levels of triglycerides, apolipoproteins AI, A-II, B, E and C-III. Both HNF1α and HNF4α dysfunctiona are associated with risk of postransplantational diabetes.

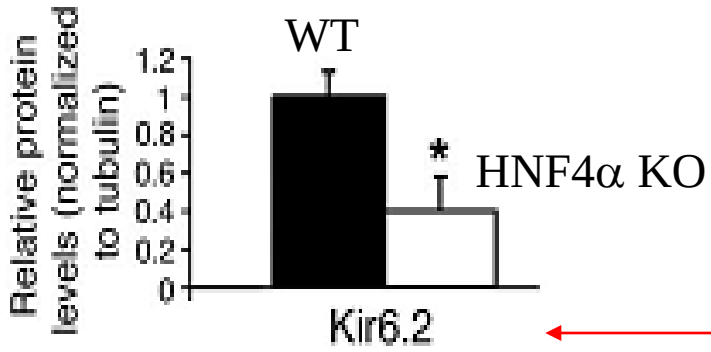


Borlak & Niechow 2009

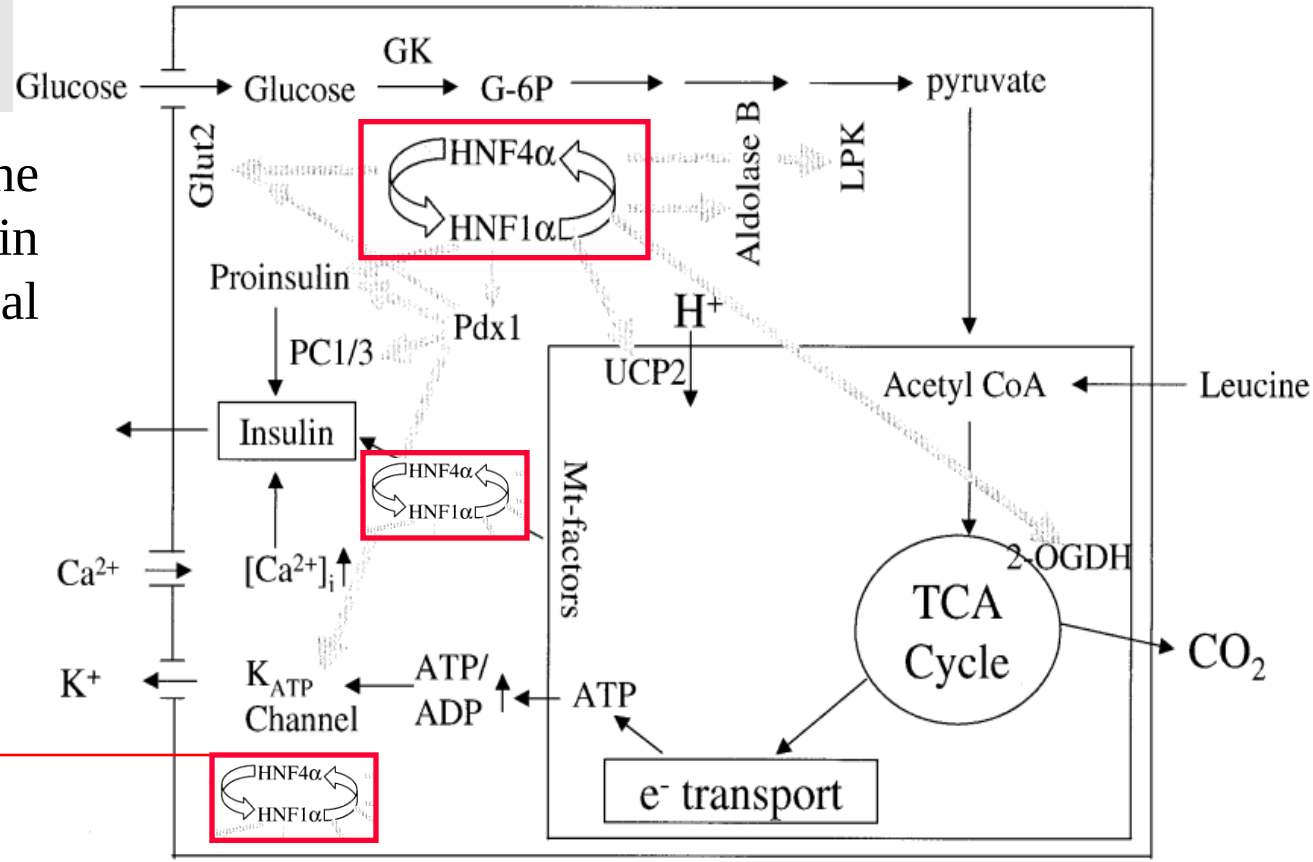


Glucose is converted into pyruvate through glycolysis and is transported into the mitochondria as a substrates to TCA cycle. ATP:ADP ratio increases and causes closure of KATP channels, depolarization of the plasma membrane, and opening of voltage-sensitive Ca2+ channels. The rising of Ca2+ evokes exocytosis of insulin.

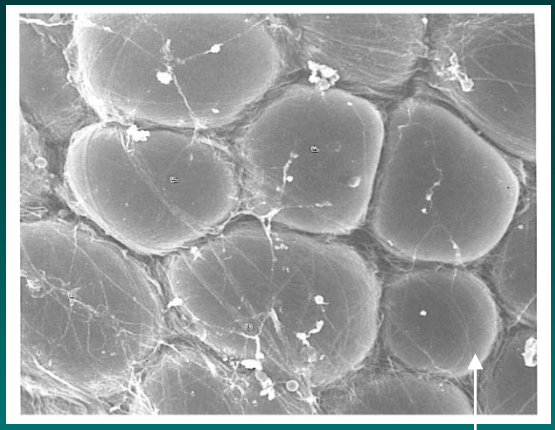
HNF-4α and HNF-1α regulate the expression of genes implicated in glycolysis and mitochondrial metabolism.



Wang et al. 2002, Gupta et al. 2005



Thank you and see you next week...



What would be profitable to remember in June:

- Expression pattern and physiological role of PPARs
- Current and potential usage of PPARα ligand in the clinic
- Potential clinical significance of PPARβ
- Nuclear receptors associated with MODY

Slides can be found in the library and at the Heme Oxygenase Fan Club page:

https://biotka.mol.uj.edu.pl/~hemeoxygenase