NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF MEDICINE

BIOCHEMISTRY II – 3nd SEMESTER

Metabolic correlations: Type 1 and 2 diabetes mellitus. Hyperglycemic-hyperosmotic coma.

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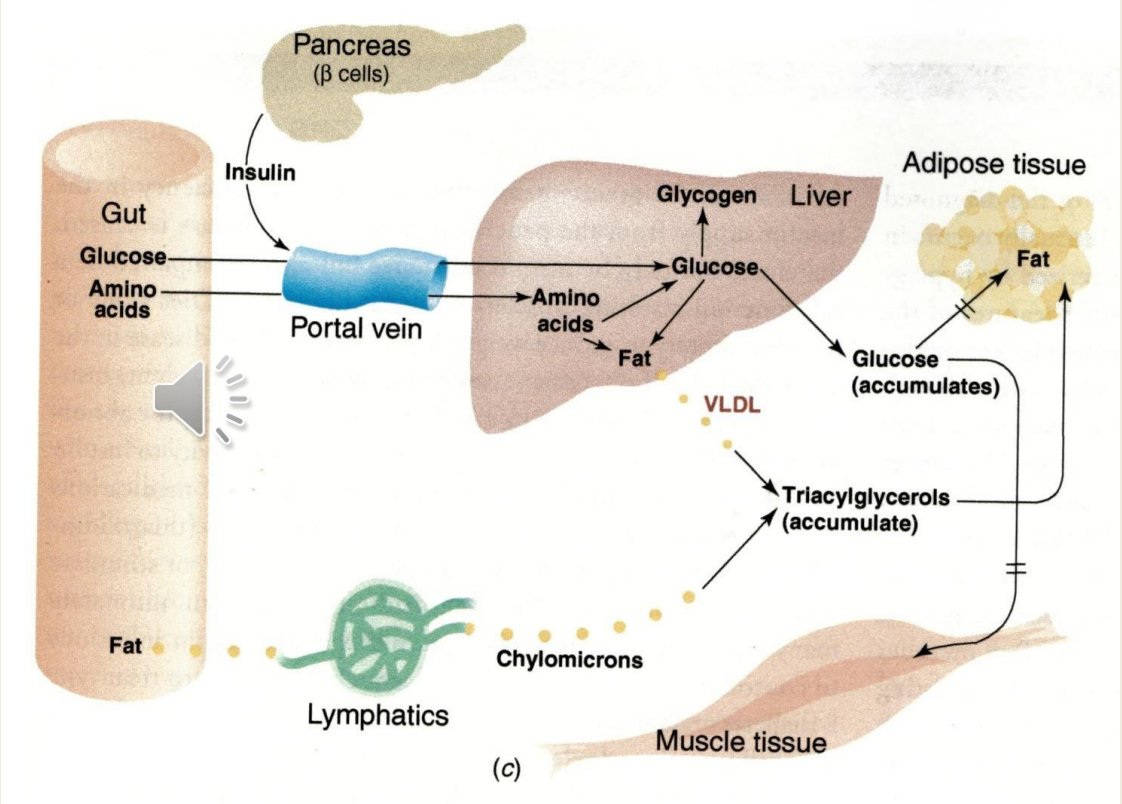
Metabolic correlations: Type 1 and 2 diabetes mellitus. Hyperglycemic-hyperosmotic coma.

Learning aims

- Understand and describe metabolic interrelationships of tissues in type 2 diabetes mellitus
- Understand and describe metabolic interrelationships of tissues in type 1 diabetes mellitus
- Describe mechanisms of obesity and the metabolic syndrome
- Describe hyperglycemic-hyperosmotic coma

Type 2 diabetes

- 80-90% diagnosed cases of diabetes
- Middle-aged
- Older obese people
- Hyperglycemia
- Often hypertriglyceridemia
- Features of the metabolic syndrome
- Transient episodes of ketoacidosis
- Type 1 diabetes complications
  - Nerve
  - Eye
  - Kidney
  - Coronary artery disease

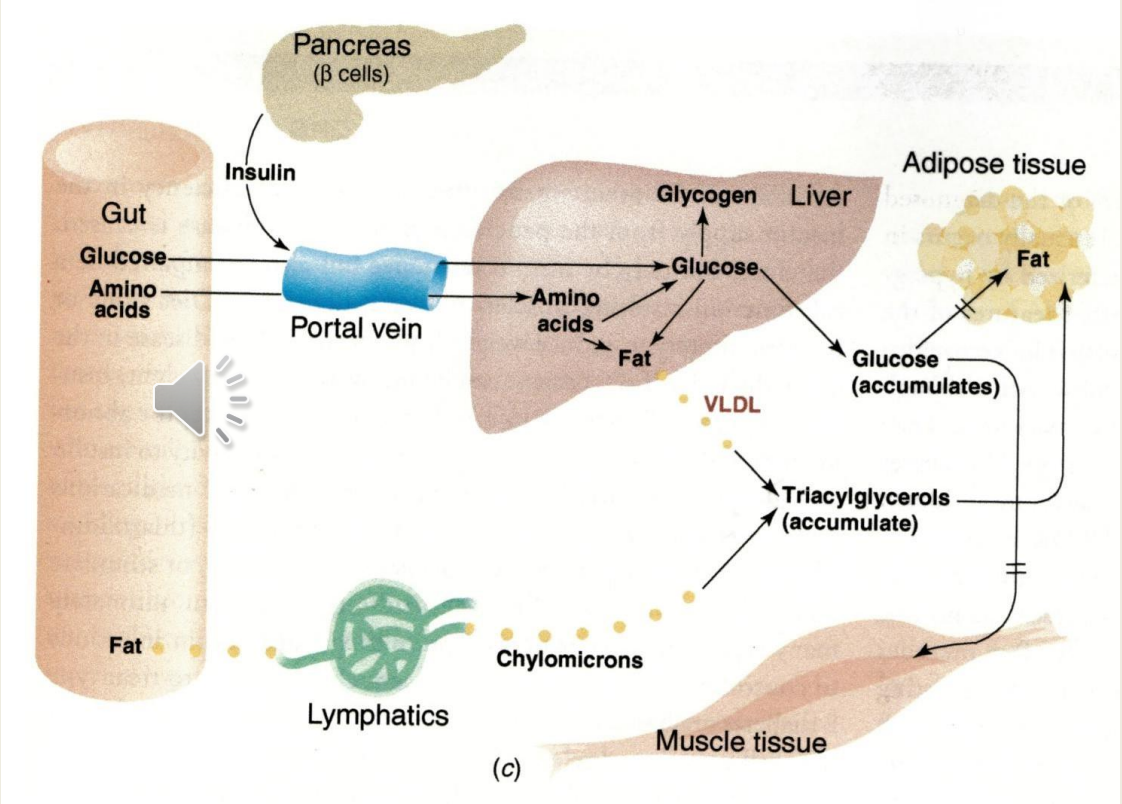


Type 2 Diabetes

- Type 2 diabetes is slow to develop (typically in older, obese individuals),
- The symptoms are milder and often go unrecognized at first.
- The regulatory activity of insulin is disordered: insulin is produced, but some feature of the insulin-response system is defective.

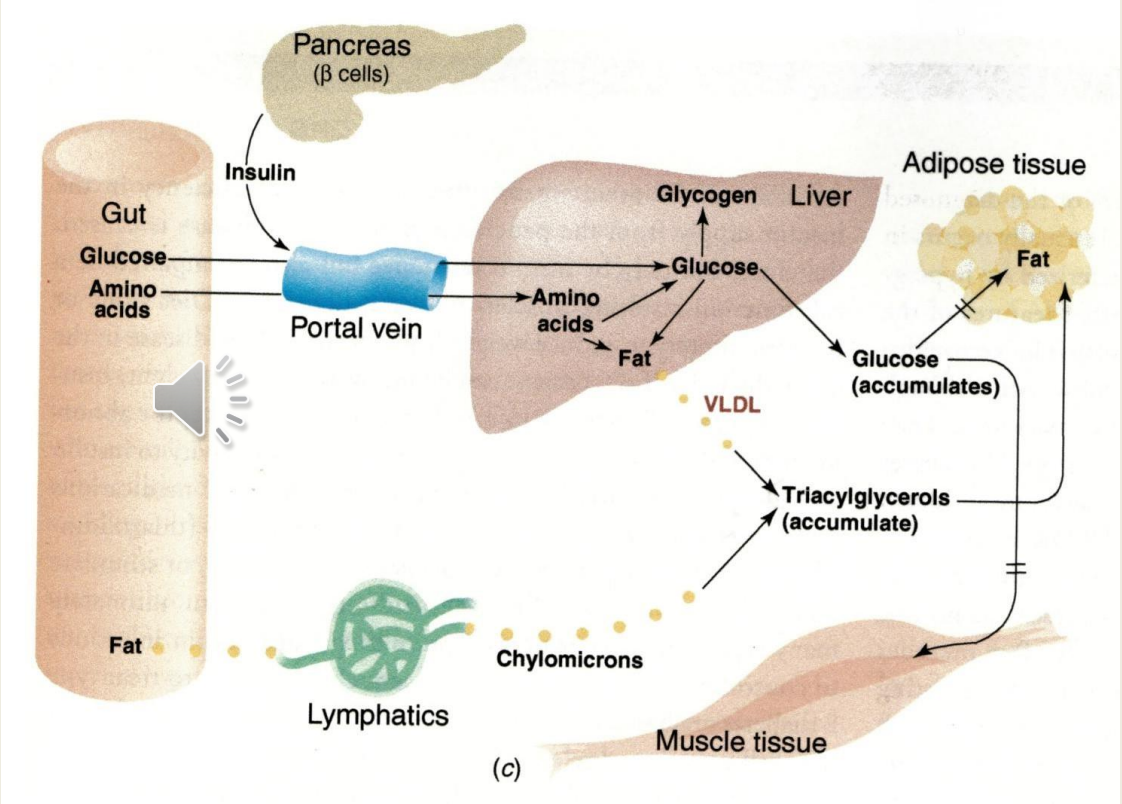
Type 2 diabetes

- **Increased VLDL as a result of:**
  - **Increased hepatic triacylglycerol synthesis**
  - **Hyperglycemia**
  - **Hyperinsulinemia**
- **Obesity is the major contributing factor**
- **Hyperinsulinemia**
- **High levels of free fatty acids**
- **Increased TNFα, resistin**
- **Low adiponectin**
- **High insulin / fewer receptors / defects of glucose transporters**
- **High insulin / high glucose**



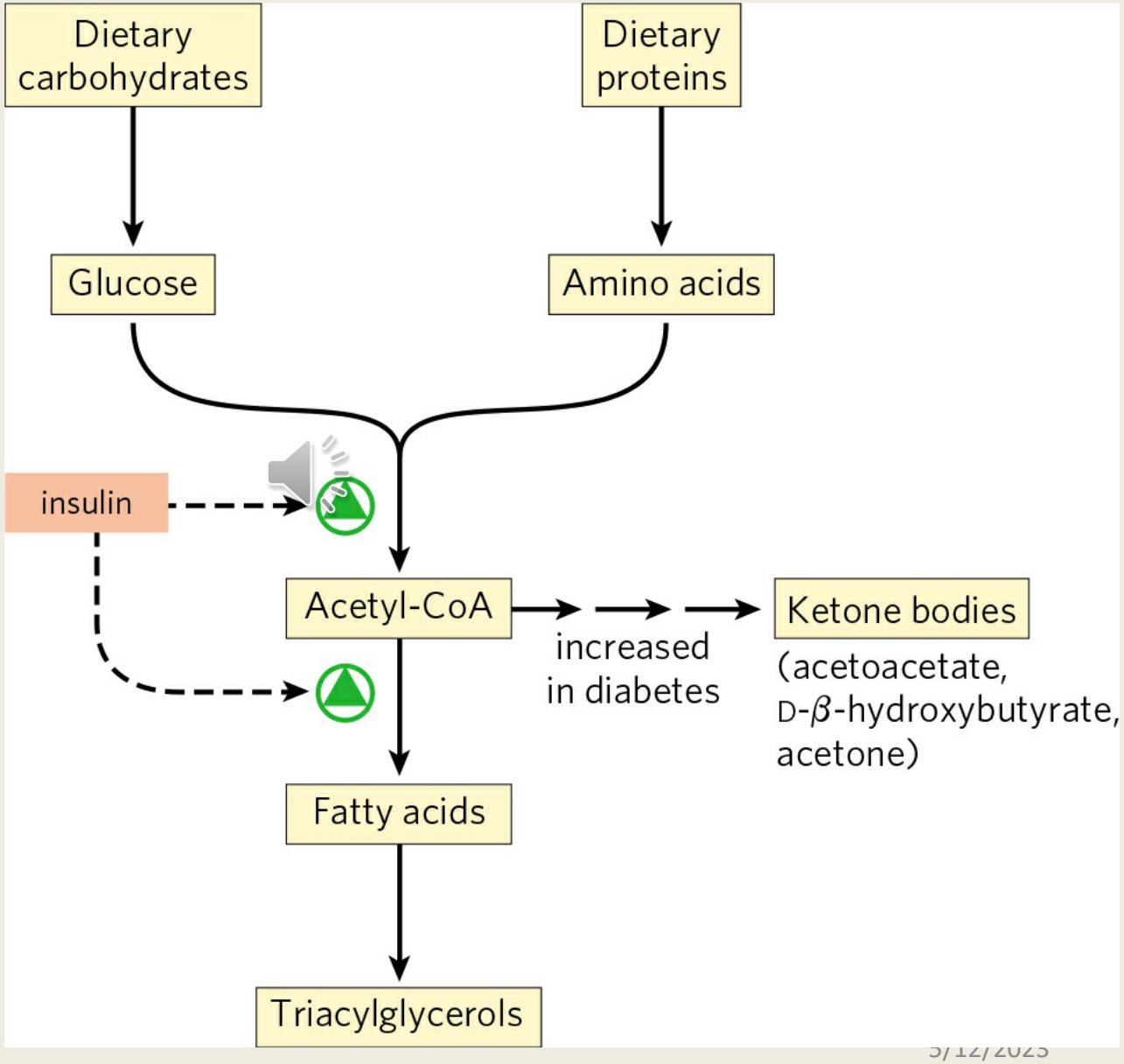
Type 2 diabetes

- Deficiency of insulin supply form the pancreatic β cells
- Insulin resistance + insulin deficiency
- Medication
  - Sensitize peripheral tissue to insulin action (thiazolidinediones - glitazones)
  - Reduce hepatic gluconeogenesis (metformin)
  - Stimulate insulin secretion (sulfonylureas)
  - Stimulation of beta cell growth and release of insulin caused by incretin/glucagon-like peptide-1, GLP-1 (increase of glucose-stimulated insulin release)
  - reducing renal tubular glucose reabsorption [Sodium-glucose cotransporter 2 (SGLT2) inhibitors]

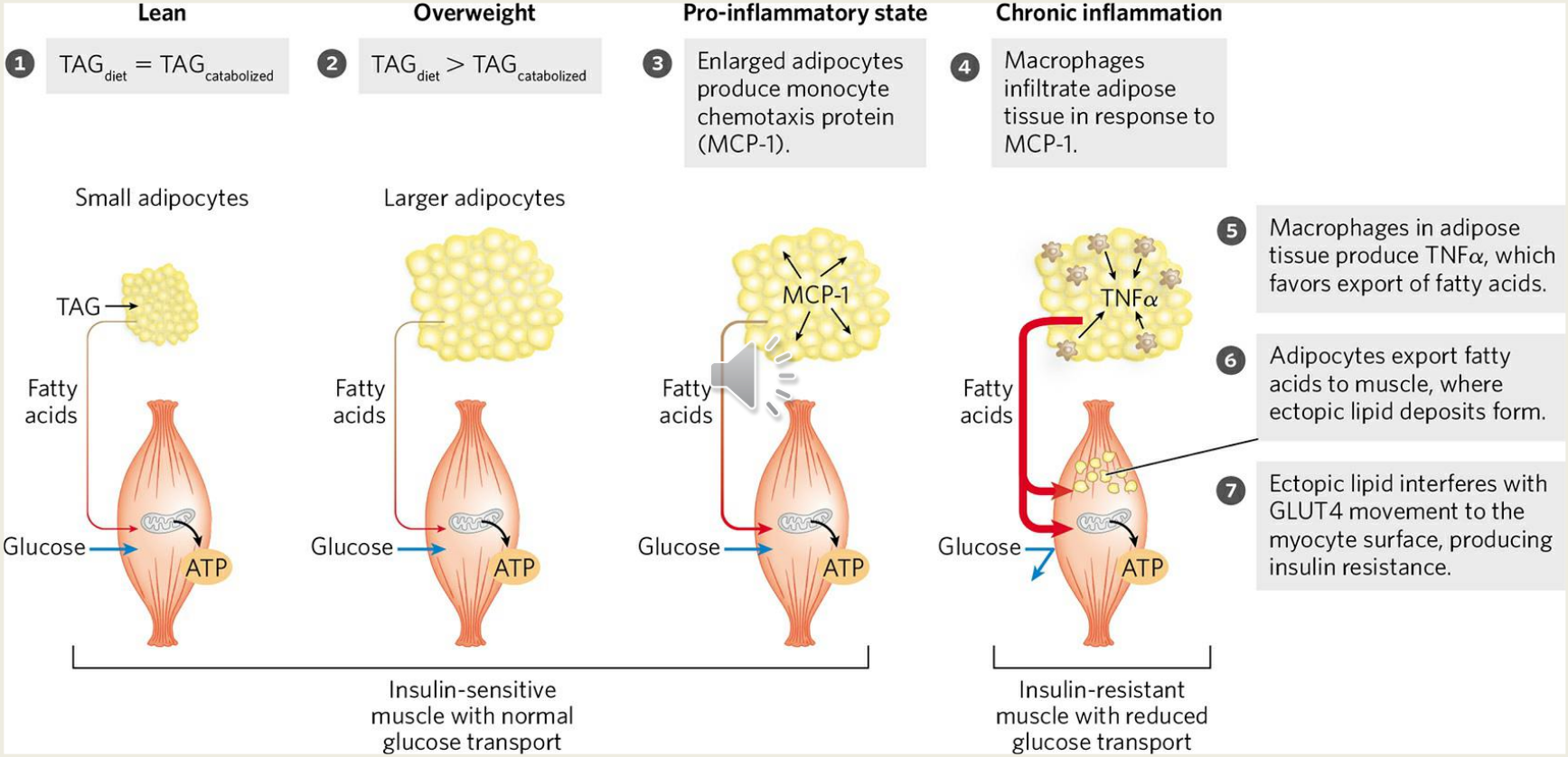


Regulation of triacylglycerol synthesis by insulin

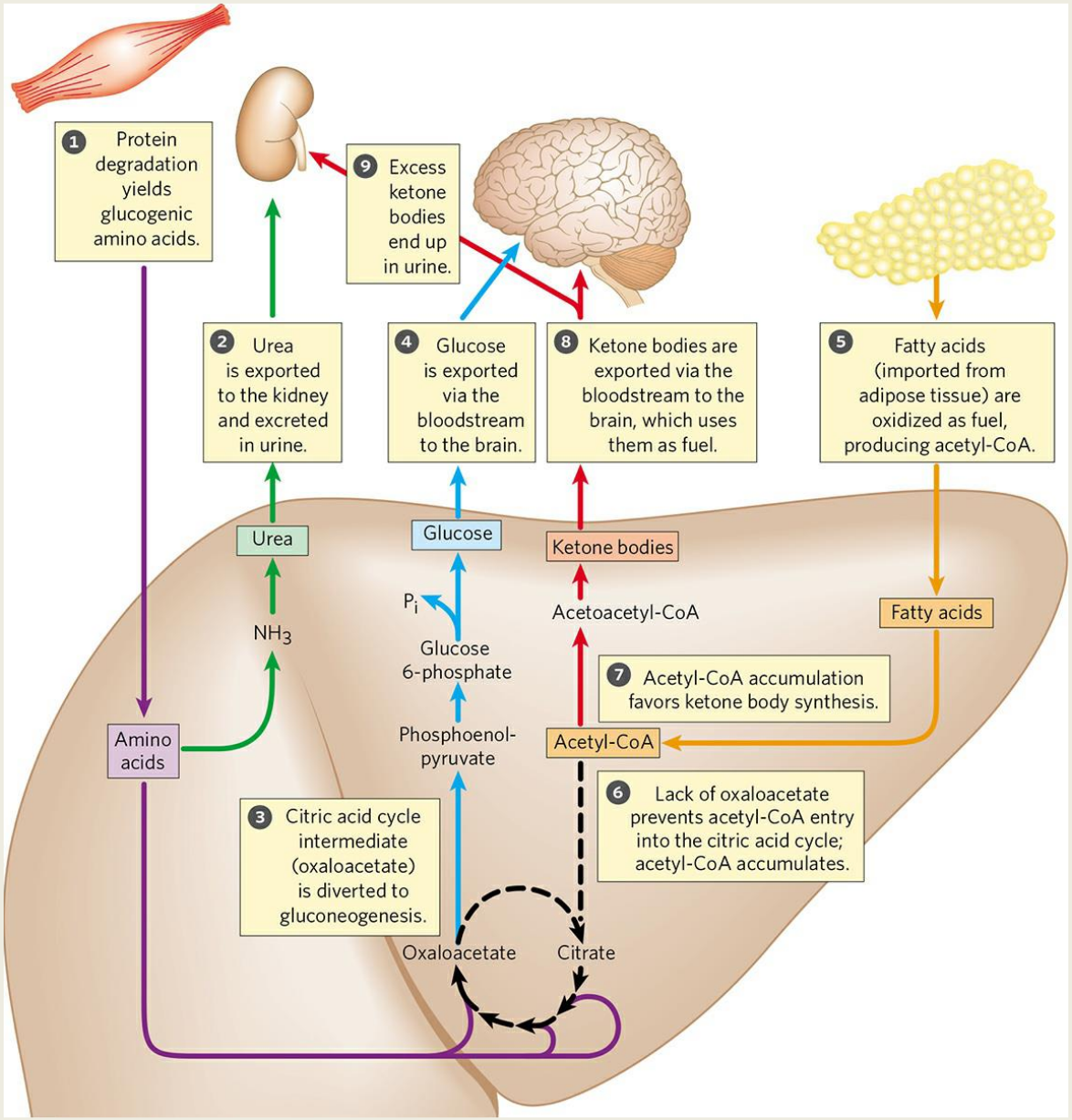
- ***Insulin stimulates***
- ***conversion of dietary carbohydrates and proteins to fat.***
- ***lack insulin or are insensitive to it.***
- ***Diminished fatty acid synthesis,***
- ***acetyl-CoA arising from catabolism of carbohydrates and proteins is directed to ketone body production***



In Type 2 Diabetes the Tissues Become Insensitive to Insulin

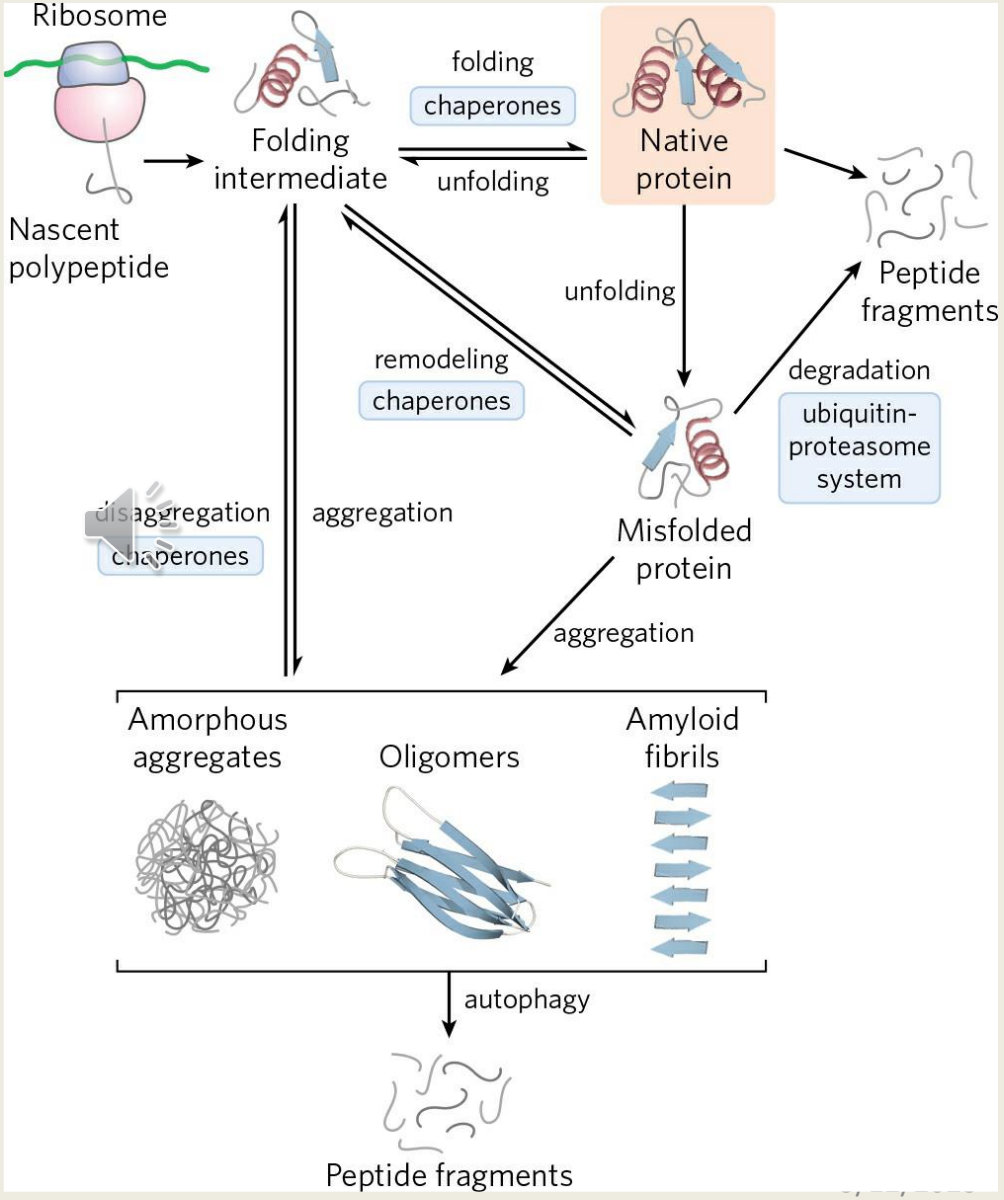


Fuel metabolism in the liver during prolonged fasting or in uncontrolled diabetes mellitus



Type 2 diabetes – protein misfolding

- **Defective proteostasis**
- **Misfolded proteins**
- **Aggregation of misfolded proteins**
- **Secretion into a misfolded insoluble extracellular amyloid-like fiber**



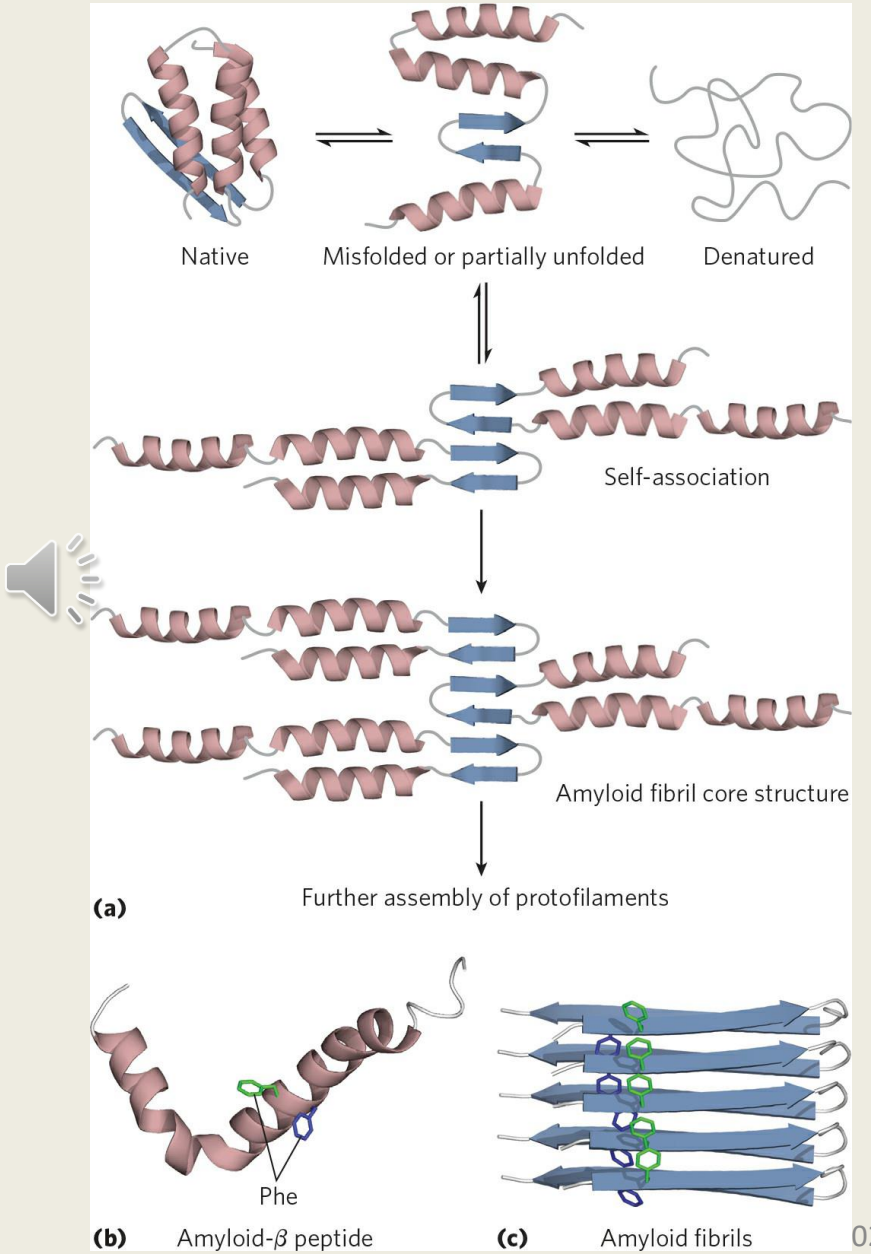
Type 2 diabetes – protein misfolding

- ***Amyloidoses (Defective systems - amyloid-related diseases)***
- ***Misfolding mechanism: type 2 diabetes, Alzheimer's, Huntington's, Parkinson's***

Defects in

- **Autophagy**
- **ubiquitin-proteasome system**
- **unfolded protein response (UPR)**

- **proteins destined for secretion undergo their initial folding in the endoplasmic reticulum**
- **stress conditions (ER stress)**
- **trigger the set of transcriptional regulators (UPR)**
- **bring the various systems into alignment by increasing the concentration of chaperones in the ER or**
- **decreasing the rate of overall protein synthesis, or**
- **Both**

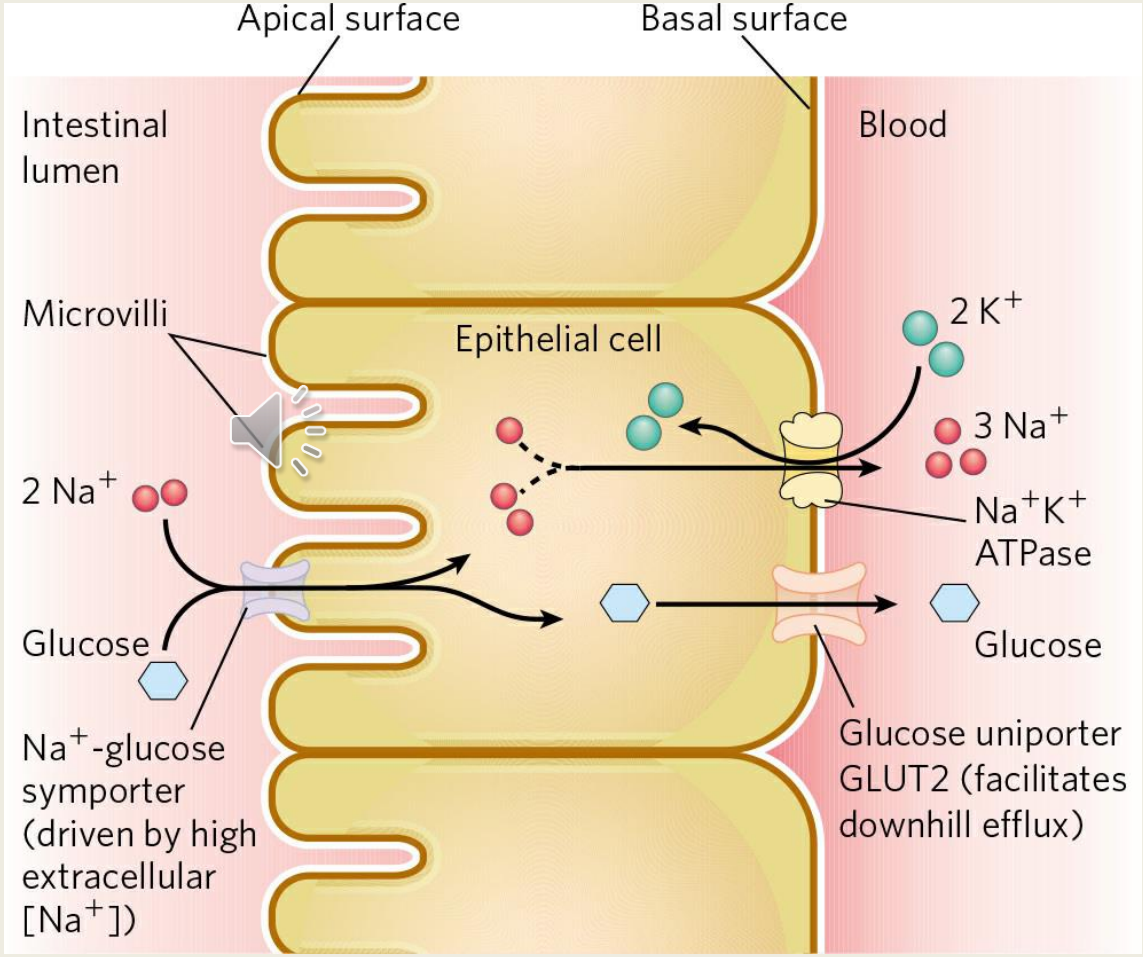


Type 2 diabetes – protein misfolding

- Amyloid deposition near the pancreatic *β* cells
- a small (37 amino acid) peptide called islet amyloid polypeptide (IAPP), or amylin, can lead to amyloid deposits around the islets, gradually destroying the cells.
- A healthy human adult has 1 to 1.5 million pancreatic *β* cells.
- With progressive loss of these cells, glucose homeostasis is affected and eventually, when
- 50% or more of the cells are lost, the condition matures into type 2 (non-insulin-dependent) diabetes mellitus.

Drugs against Type 2 Diabetes – SGLT2

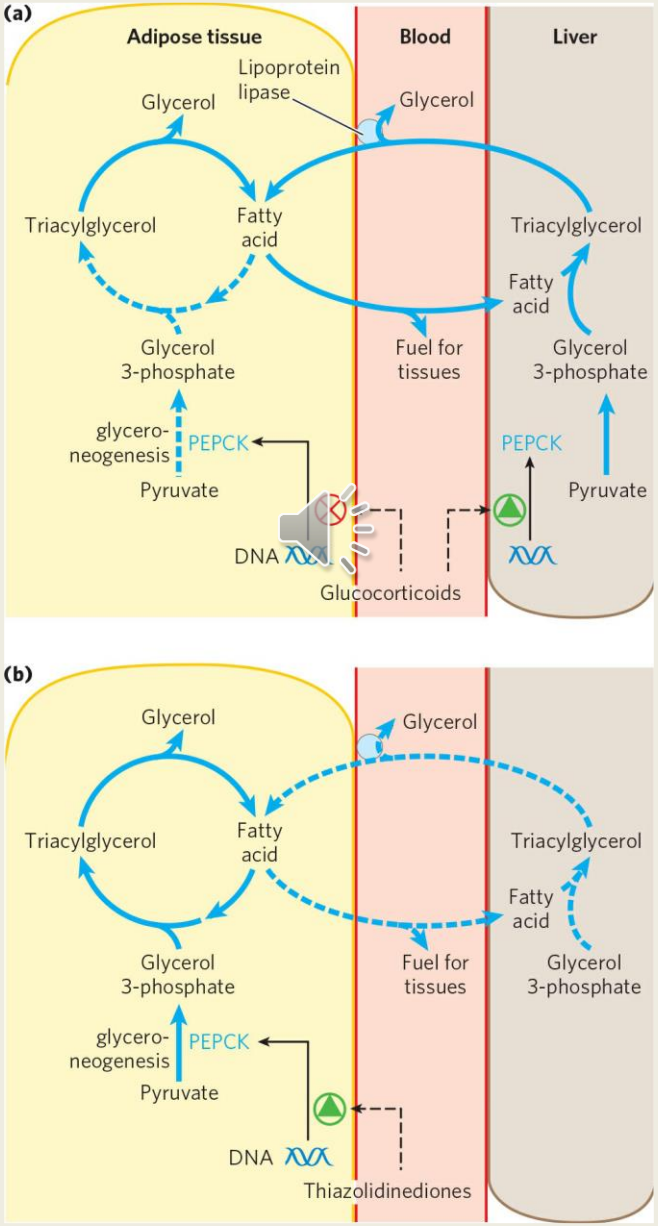
- ***Nα participates in absorption of glucose from the intestinal cells and release to the blood circulation***
- ***In the kidney, a different Na+-glucose symporter is the target of drugs used to treat type 2 diabetes.***
- ***Glifozins are specific inhibitors of this Na+-glucose symporter***
- ***Inhibit glucose reabsorption in the kidney***
- ***It is cleared in the urine***



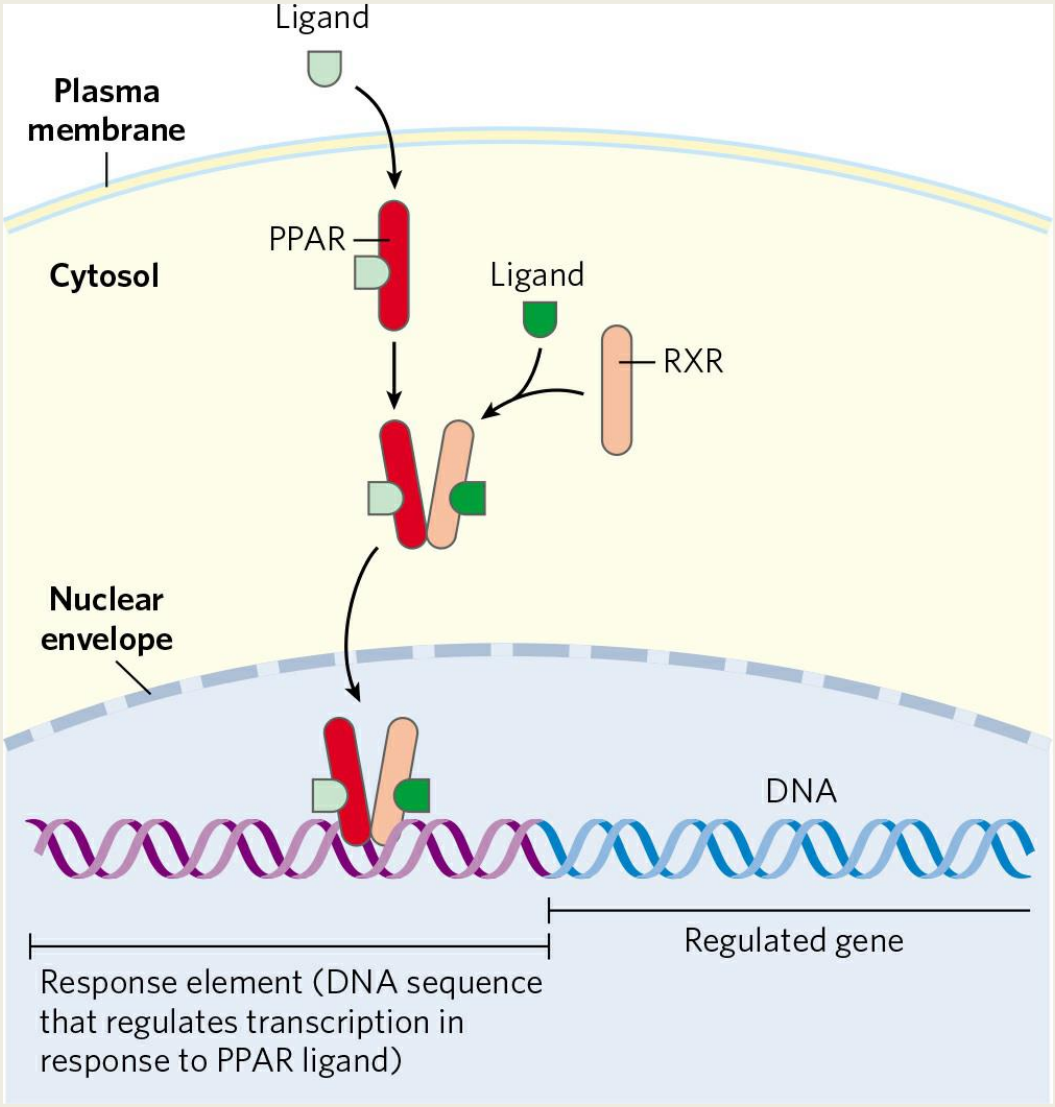
Thiazolidinediones Treat Type 2 Diabetes by Increasing Glyceroneogenesis

- High levels of free fatty acids in the blood interfere with glucose utilization in muscle and promote the insulin resistance that leads to type 2 diabetes.
- reduce the levels of fatty acids circulating in the blood and increase sensitivity to insulin
- increase in glyceroneogenesis, which in turn increases the resynthesis of triacylglycerol in adipose tissue and reduces the release of free fatty acid from adipose tissue into the blood

Thiazolidinediones Treat Type 2 Diabetes by Increasing Glyceroneogenesis

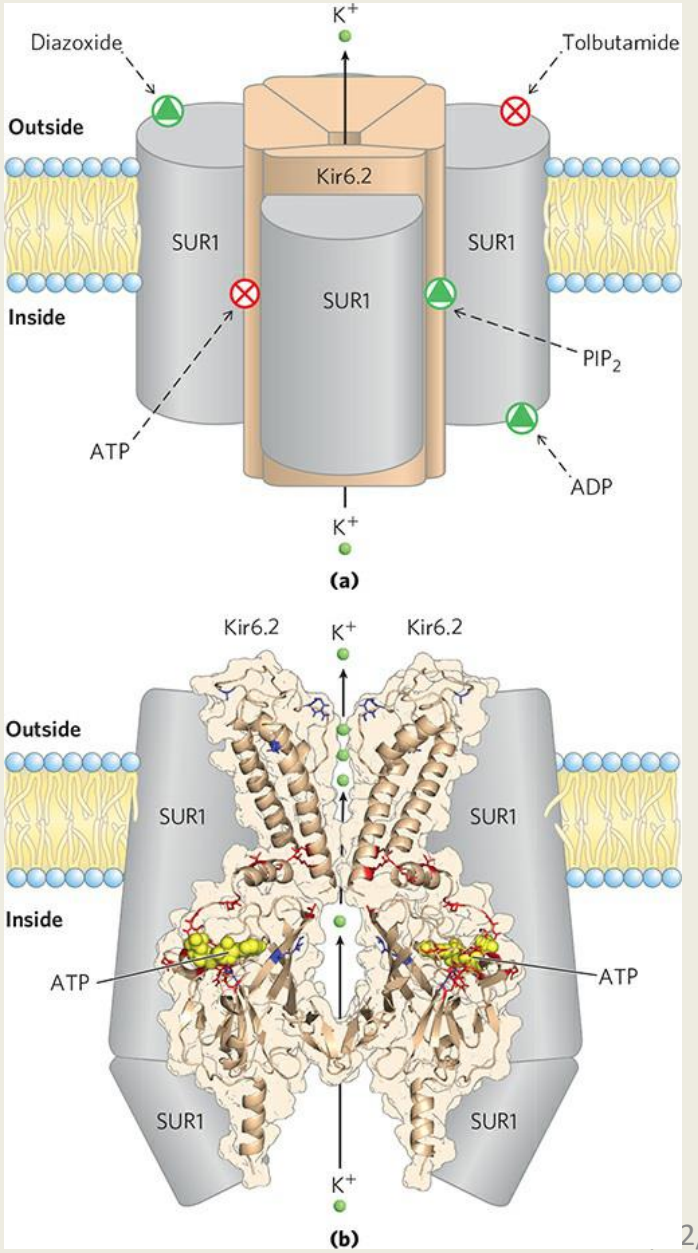


- **Proteins in a family of ligand-activated transcription factors known as peroxisome proliferator-activated receptors (PPARs) respond to changes in dietary lipid by altering the expression of genes**
- **involved in fat and carbohydrate metabolism**
- **PPARγ is activated by the thiazolidinedione drugs that are used to treat type 2 diabetes**



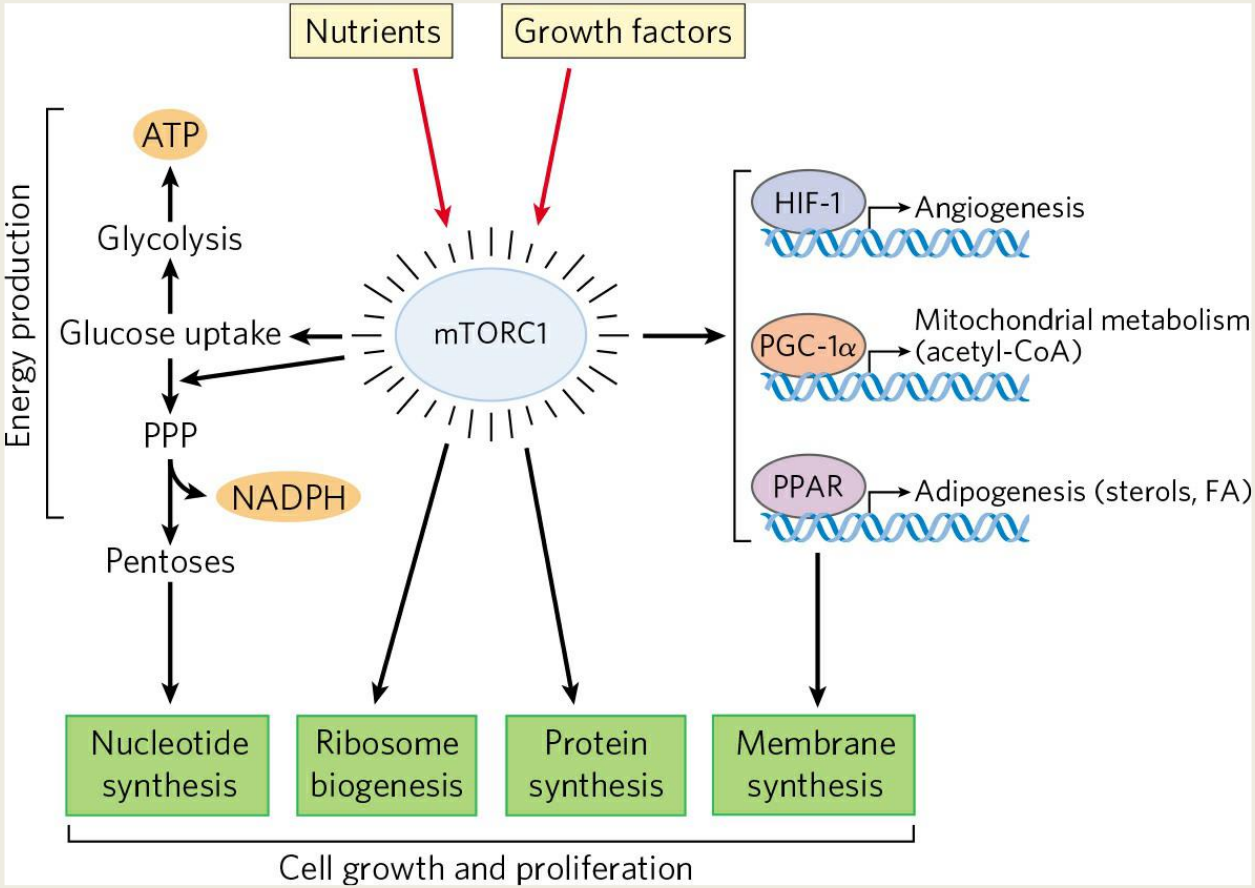
ATP-gated K+ channels in β cells

- ***sulfonylurea drugs***
- ***Bind to the SUR1 (sulfonylurea receptor) subunits of the K+ channels, closing the channels and stimulating insulin release***
- ***Mutation in certain amino acid residues (shown in red) leads to neonatal diabetes; mutation in others (shown in blue) leads to hyperinsulinism of infancy.***

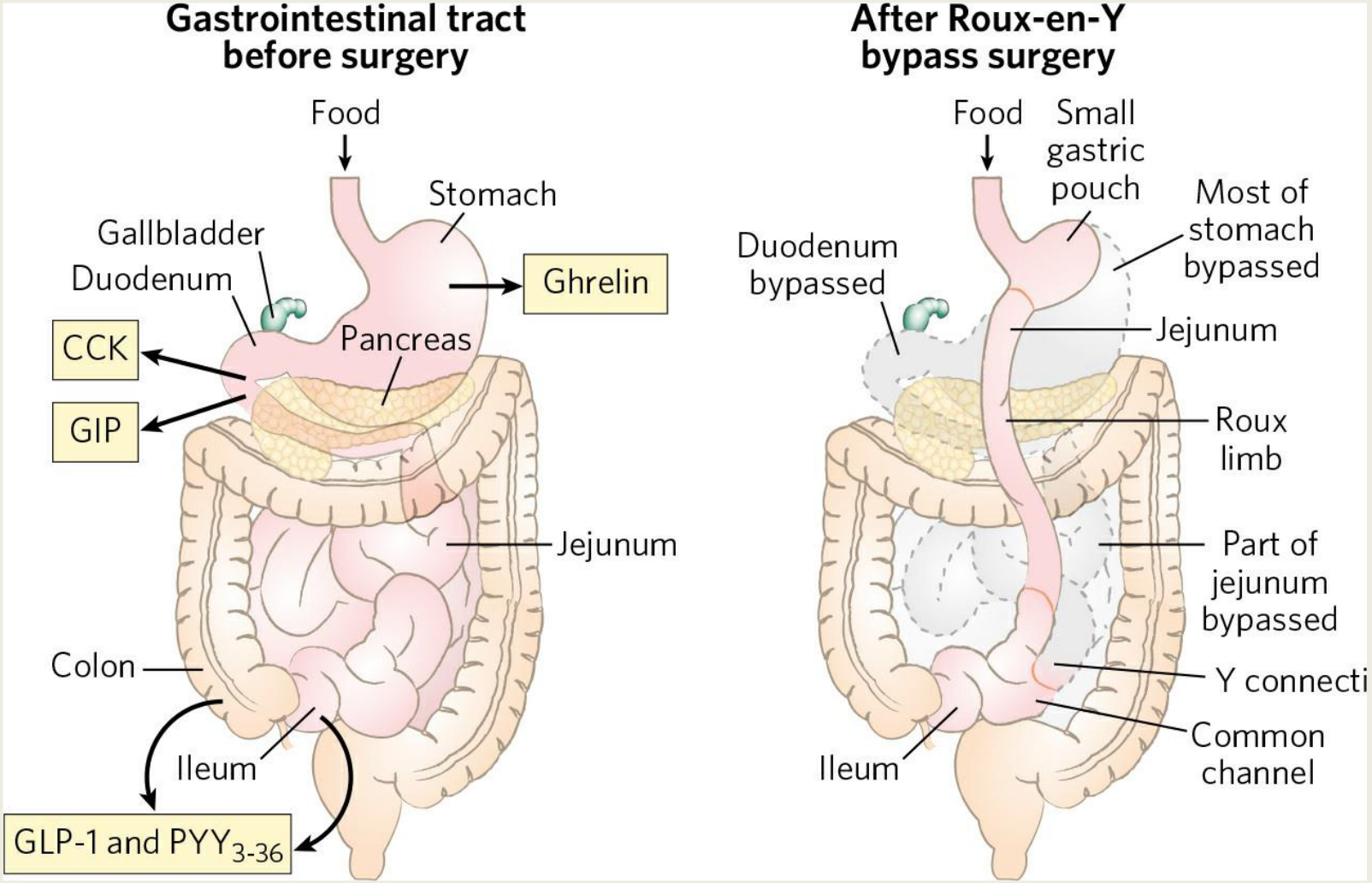


mTORC1 stimulates cell growth and proliferation when adequate nutrition is available

Chronic activation of mTORC1 by overeating results in excess deposition of TAGs in adipose tissue, as well as in liver and muscle, which may contribute to insulin insensitivity and type 2 diabete



Type 2 Diabetes Is Managed with Diet, Exercise, Medication, and Surgery



Type 2 Diabetes Is Managed with Diet, Exercise, Medication, and Surgery

TABLE 23-8 Treatments for Type 2 Diabetes Mellitus

Intervention/treatment	Direct target	Effect of treatment
Weight loss	Adipose tissue; reduce TAG content	Reduces lipid burden; increases capacity for lipid storage in adipose tissue; restores insulin sensitivity
Exercise	AMPK, activated by increasing [AMP]/[ATP]	Aids weight loss (see Fig. 23-39)
Bariatric surgery	Unknown	Leads to weight loss, better control of blood glucose
Sulfonylureas: glipizide (Glucotrol), glyburide (Micronase), glimepiride (Amaryl)	Pancreatic β cells; K^+ channels blocked	Stimulates insulin secretion by pancreas (see Fig. 23-28)
Biguanides: metformin (Glucophage)	AMPK, activated	Increases glucose uptake by muscle; decreases glucose production in liver
Thiazolidinediones: troglitazone (Rezulin),[a] rosiglitazone (Avandia),[b] pioglitazone (Actos)	PPARγ	Stimulates expression of genes, potentiating the action of insulin in liver, muscle, adipose tissue; increases glucose uptake; decreases glucose synthesis in liver
GLP-1 modulators: exenatide (Byetta), sitagliptin (Januvia)	Glucagon-like peptide-1, dipeptide protease IV	Enhances insulin secretion by pancreas

[a] Voluntarily withdrawn because of side effects.

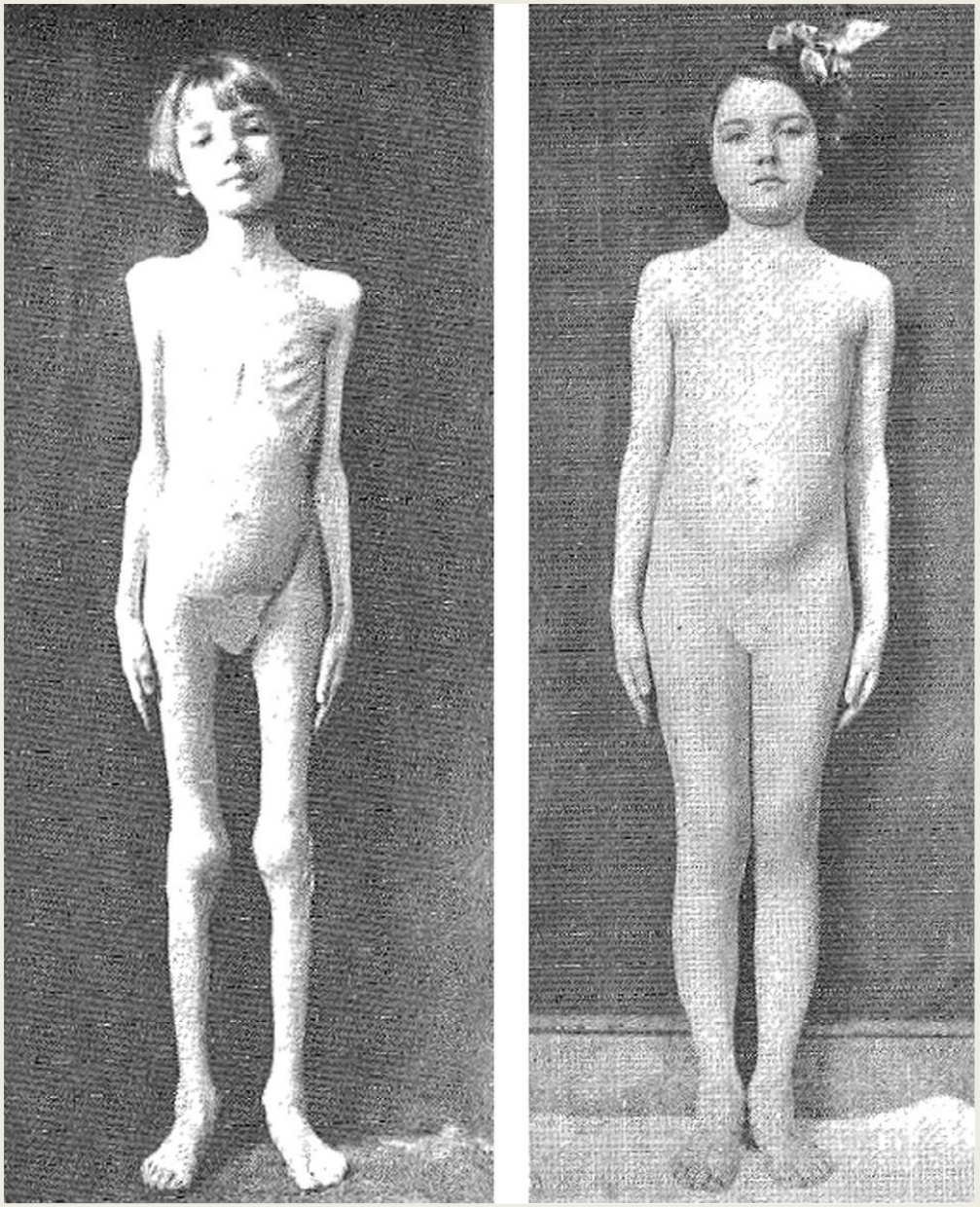
[b] Prescriptions limited to patients not helped by other treatment, because of possible increased risk of cardiovascular disease.

Type I Diabetes

- **Usually begins early in life, and symptoms quickly become severe**
- **responds to insulin injection, because the metabolic defect stems from an autoimmune destruction of pancreatic *β* cells and a consequent inability to produce sufficient insulin.**
- **Type 1 diabetes requires both insulin therapy and careful, lifelong control of the balance between dietary intake and insulin dose.**
- **Characteristic symptoms of type 1 (and type 2) diabetes are excessive thirst and frequent urination (polyuria), leading to the intake of large volumes of water (polydipsia).**
- **("Diabetes mellitus" means "excessive excretion of sweet urine.")**

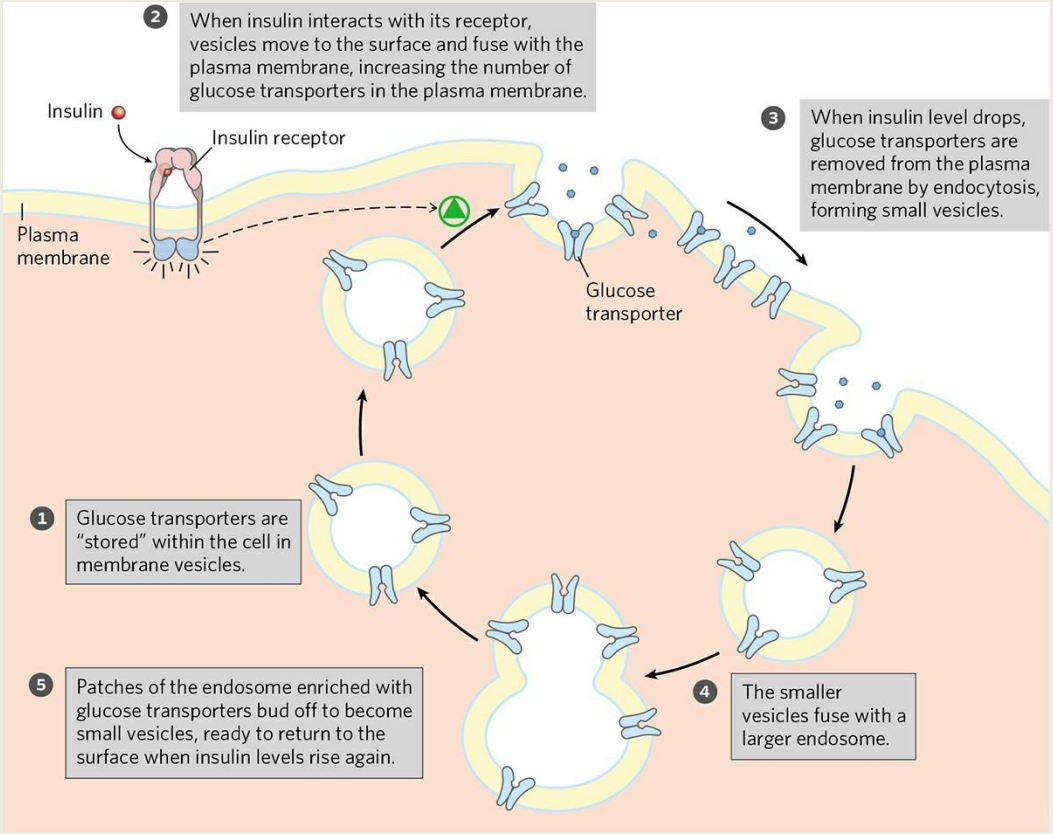
- **These symptoms are due to excretion of large amounts of glucose in the urine, a condition known as glucosuria.**

Type I Diabetes



Defective Glucose Transport in Diabetes

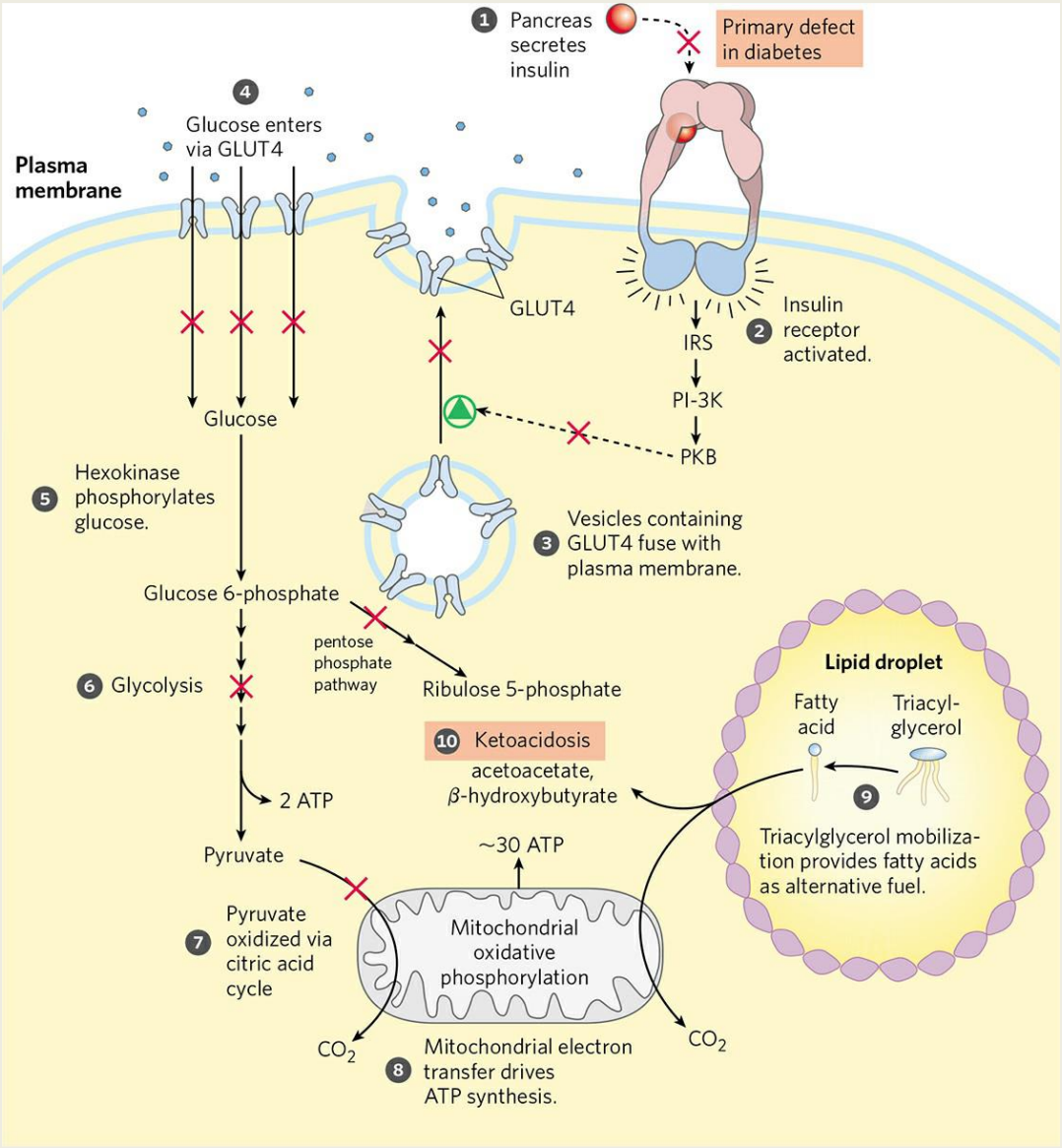
- **In type 1 (insulin-dependent) diabetes mellitus, the inability to release insulin (and thus to mobilize glucose transporters) results in low rates of glucose uptake into muscle and adipose tissue.**



Deficient glucose uptake in Type 1 Diabetes

- Pancreas has too few β cells and cannot release sufficient insulin to trigger glucose uptake by the cells of skeletal muscle, heart, or adipose tissue.
- glucose accumulates to abnormally high levels in the blood, a condition known as hyperglycemia
- muscle and fat tissue use the fatty acids of stored triacylglycerols as their principal fuel
- In the liver, acetyl-CoA derived from this fatty acid breakdown is converted to “ketone bodies”—acetoacetate and β-hydroxybutyrate—which are exported and carried to other tissues to be used as fuel
- In untreated type 1 diabetes, overproduction of acetoacetate and β-hydroxybutyrate leads to their accumulation in the blood, and the consequent lowering of blood pH produces ketoacidosis
- Insulin injection reverses this sequence of events: GLUT4 moves into the plasma membranes of hepatocytes and adipocytes, glucose is taken up into the cells and phosphorylated, and the blood glucose level falls, greatly reducing the production of ketone bodies.

Effect of type I diabetes on carbohydrate and fat metabolism in adipocytes

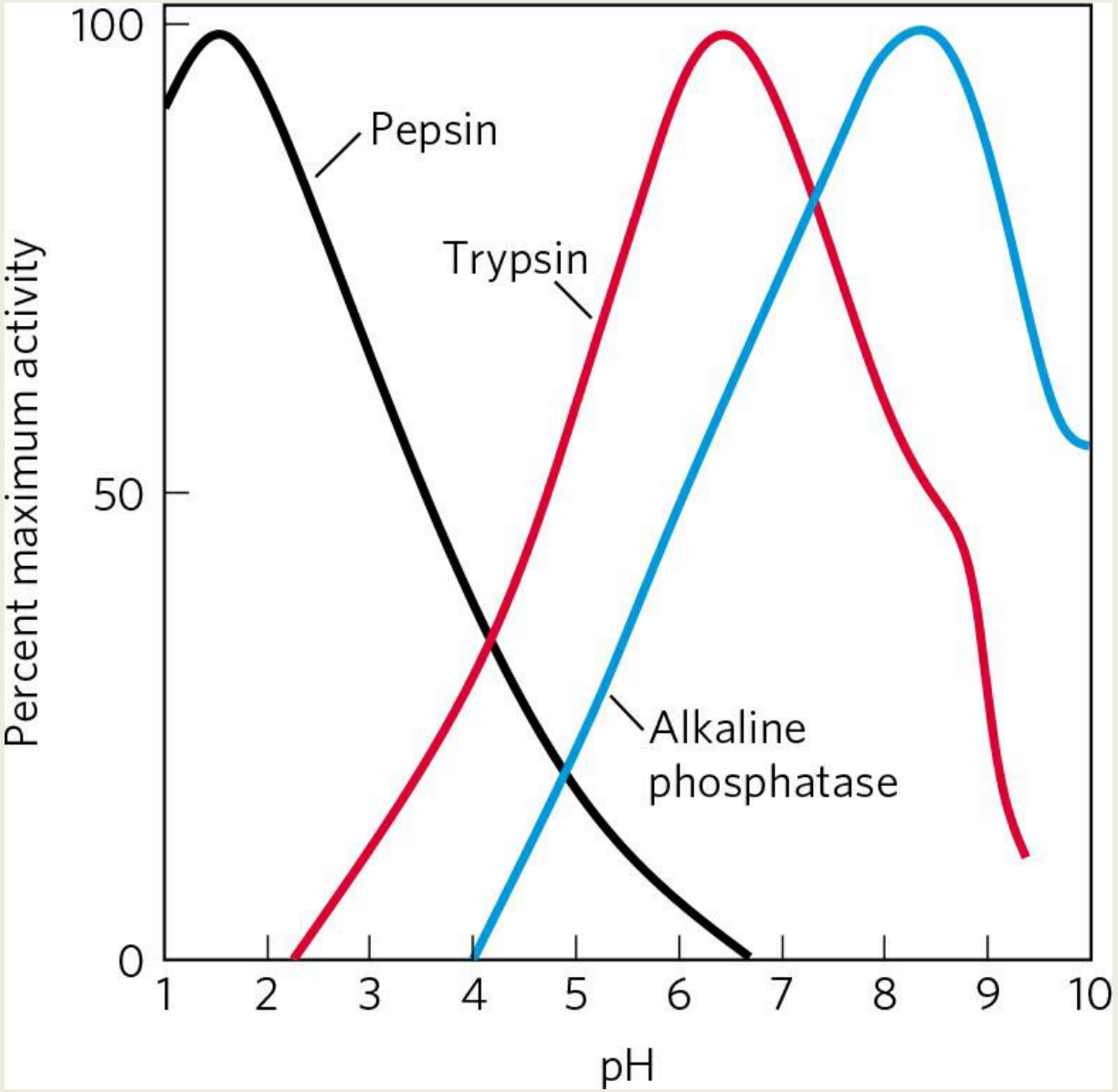


Diabetes mellitus diagnosis

- **High blood glucose**
- **Low plasma pH**
- **High levels of β-hydroxybutyric acid and acetoacetic acid in blood and urine**

Acidosis in Diabetes

The pH optima of some enzymes



Acidosis in Diabetes

- **Normal pH 7.35-7.45**
- **a small change in pH can make a large difference in the rate of some crucial enzyme-catalyzed reactions**
- **Lack of insulin or insensitivity to insulin**
- **Tissues use stored fatty acids**
- **High ketone bodies (β-hydroxybutyric acid and acetoacetic acid)**
- **Blood: 90 mg/100 mL, compared with <3 mg/100 mL in control (healthy) individuals**
- **urinary excretion of 5 g/24 hr, compared with <125 mg/24 hr in controls**
- **pH<7.35 / acidosis**
- **People in severe ketosis smell of acetone, so the condition is sometimes mistaken for drunkenness**

Acidosis in Diabetes

- **Severe acidosis**:
- Headache
- Drowsiness
- Nausea
- Vomiting
- Diarrhea
- Stupor
- Coma
- convulsions,
- some enzyme(s) do not function optimally

Diabetes mellitus diagnosis

- High blood glucose
- Low plasma pH
- High levels of β-hydroxybutyric acid and acetoacetic acid in blood and urine
- Treatment of the underlying condition—administering insulin to people with diabetes
- Severe acidosis can be reversed by administering bicarbonate solution intravenously

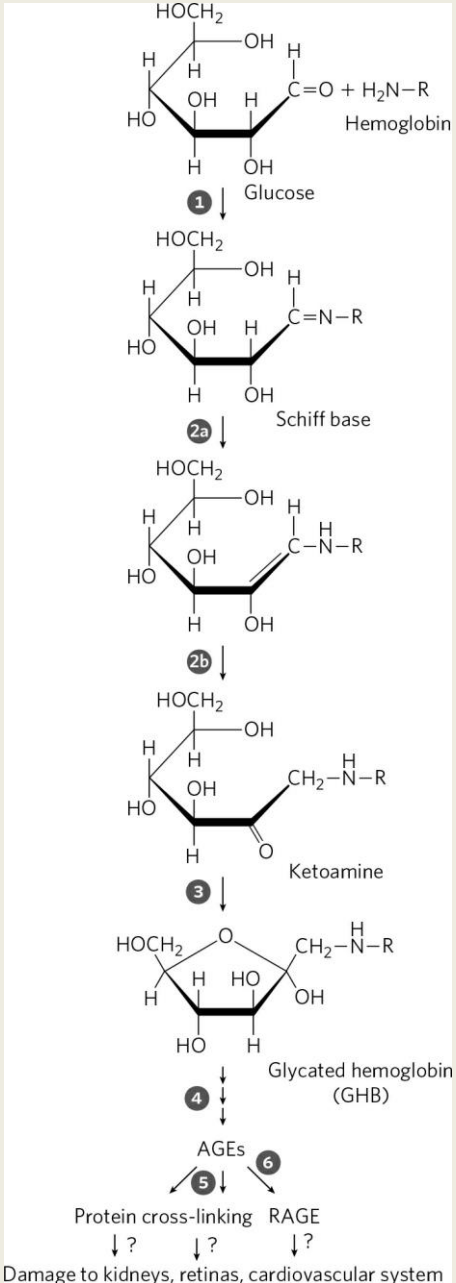
Diabetes mellitus diagnosis

- *Modern measurements require just a drop of blood, added to a test strip containing the enzyme glucose oxidase, which catalyzes the following reaction*

- *A second enzyme, a peroxidase, catalyzes reaction of the H2O2 with a colorless compound to create a colored product, which is quantified with a simple photometer that reads out the blood glucose concentration*

Diabetes mellitus diagnosis

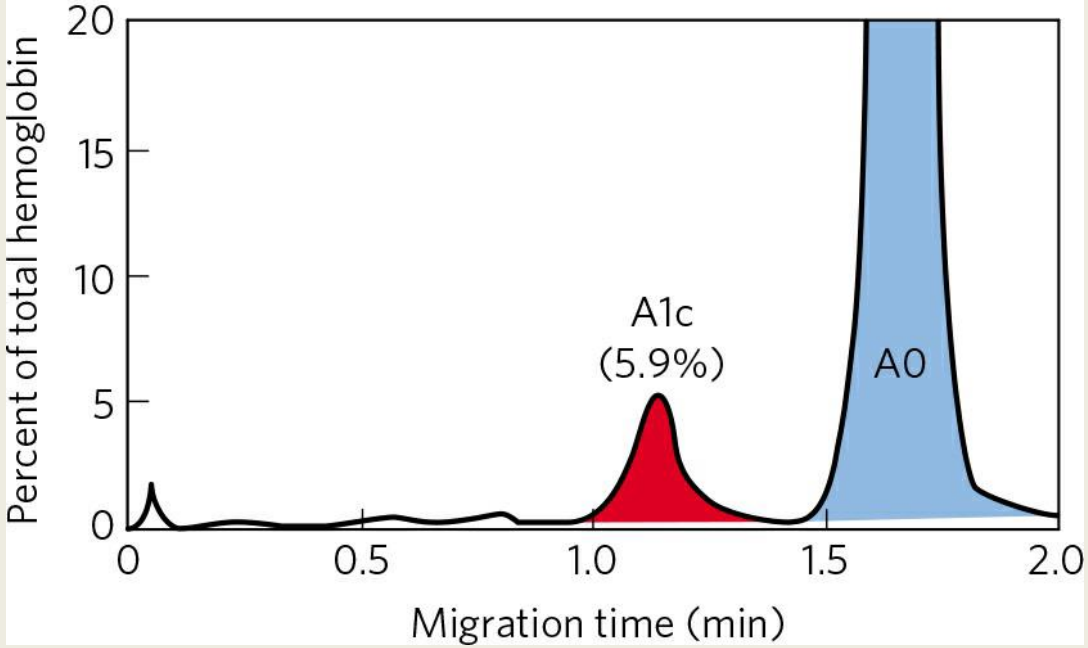
- single-time measurements do not reflect the average blood glucose over hours and days
- A nonenzymatic reaction occurs between glucose and primary amino groups in hemoglobin (either the aminoterminal Val or the ε-amino groups of Lys residues)
- The rate of this process is proportional to the concentration of glucose, so the reaction can be used to estimate the average blood glucose level over weeks
- hemoglobin glycation (HbA1c) reflects the average blood glucose concentration over the circulating “lifetime” of the erythrocyte (about 120 days)



Diabetes mellitus diagnosis

- measured clinically by extracting hemoglobin from a small sample of blood and separating GHB from unmodified hemoglobin electrophoretic ally

Analyte ID	Percent	Time (min)	Area
Injection	0.0	0.11	17,682
A1a	0.4	0.30	8,051
A1b	1.0	0.45	19,267
A1c	5.9	1.10	110,946
A0	92.6	1.56	1,727,669
		Total area	1,883,615



Genetic Mutations That Lead to Rare Forms of Diabetes

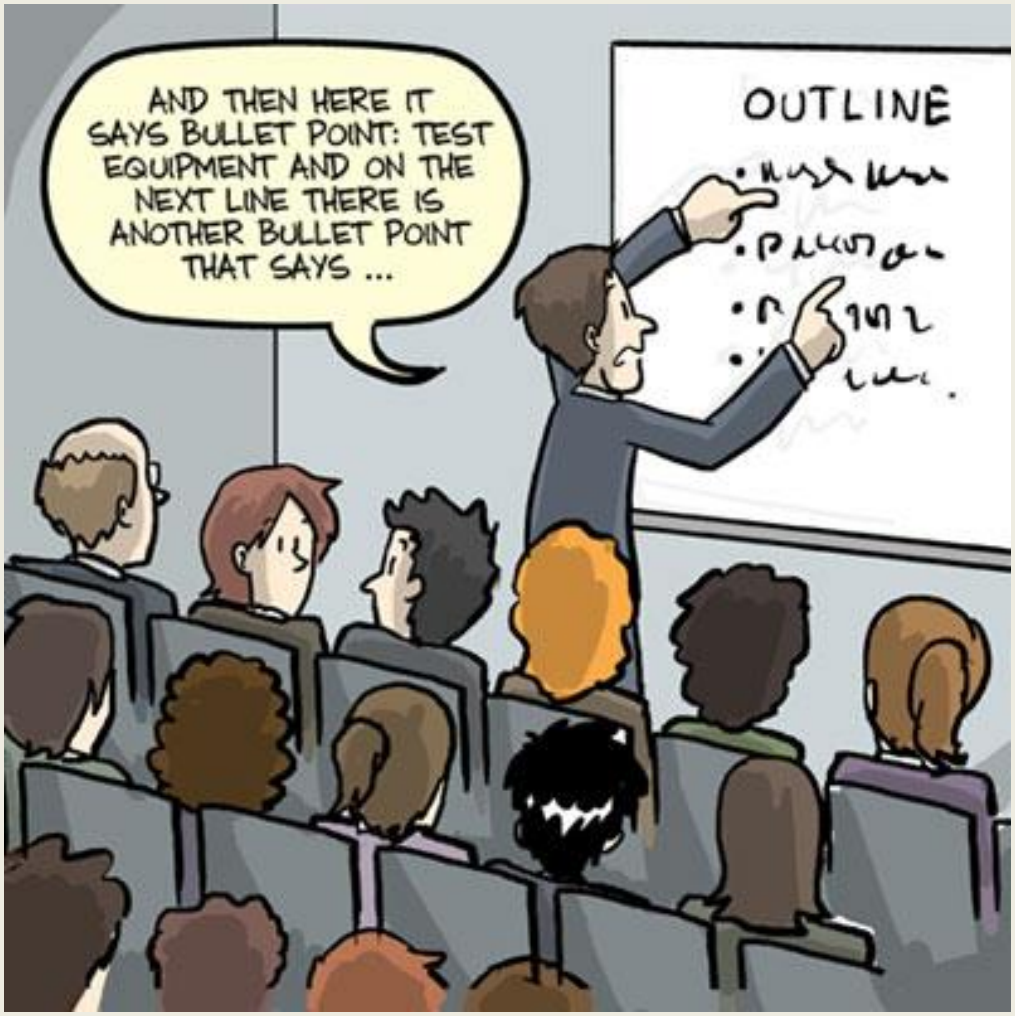
- The term “diabetes” describes a variety of medical conditions that have in common an excessive production of urine
- *diabetes insipidus*, in which defective water reabsorption in the kidney results from a mutation in the gene for aquaporin
- Type 1, also called insulin-dependent diabetes mellitus (IDDM), is caused by autoimmune attack on the insulin-producing β cells of the pancreas. Individuals with IDDM must take insulin by injection or inhalation to compensate for their missing β cells. IDDM develops in childhood or in the teen years; an older name for the disease is juvenile diabetes.
- Type 2, also called non-insulin-dependent diabetes mellitus (NIDDM), typically develops in adults over 40 years old. It is far more common than IDDM, and its occurrence in the population is strongly correlated with obesity. The current epidemic of obesity in the more developed countries brings with it the promise of an epidemic of NIDDM, providing a strong incentive to understand the relationship between obesity and the onset of NIDDM at the genetic and biochemical levels.

maturity-onset diabetes of the young (MODY)

- genetic mutation affects a transcription factor important in carrying the insulin signal into the nucleus, or affects an enzyme that responds to insulin
- **MODY2**, a mutation in the hexokinase IV (glucokinase) gene affects the liver and pancreas, tissues in which this is the main isoform of hexokinase
- individuals with inactivating mutations in both copies of the glucokinase gene have very high thresholds for insulin release, and consequently, from birth, **they have severe hyperglycemia—permanent neonatal diabetes.**
- In individuals with one mutated and one normal copy of the glucokinase gene, the glucose threshold for insulin release rises to about 7 mM. As a result**, these individuals have blood glucose levels only slightly above normal: they generally have only mild hyperglycemia and no symptoms. This condition (MODY2)** is generally discovered by accident during routine blood glucose analysis.
- There are at least five other types of MODY, each the result of an inactivating mutation in one or another of the transcription factors essential to the normal development and function of pancreatic *β* cells
- **MODY1 and MODY3**, the defects are severe enough to produce the long-term complications associated with IDDM and NIDDM—cardiovascular problems, kidney failure, and blindness
- **MODY4, 5, and 6** are less severe forms of the disease

A Rare Form of Diabetes Results from Defects in the Mitochondria of Pancreatic *β* Cells

- Pancreatic *β* cells with defects in oxidative phosphorylation cannot increase [ATP] above this threshold, and the resulting failure of insulin release effectively produces diabetes.


AND THEN HERE IT SAYS BULLET POINT: TEST EQUIPMENT AND ON THE NEXT LINE THERE IS ANOTHER BULLET POINT THAT SAYS ...
OUTLINE

Thank you!