NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF MEDICINE

BIOCHEMISTRY II – 3nd SEMESTER

# Metabolic correlations: Polyol pathway and complications of Diabetes Mellitus

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# Metabolic correlations: Polyol pathway and complications of Diabetes Mellitus

## Learning aims

- Understand and describe the polyol pathway
- Describe multi-organ complications of diabetes mellitus

# Metabolic correlations: Polyol pathway and complications of Diabetes Mellitus

## Acute metabolic complications

- diabetic ketoacidosis (hyperglycemia)
- coma (hypoglycemia)

## Long-term vascular complications

- wide range
- chronic elevation of blood glucose levels
- damage of blood vessels (angiopathy)

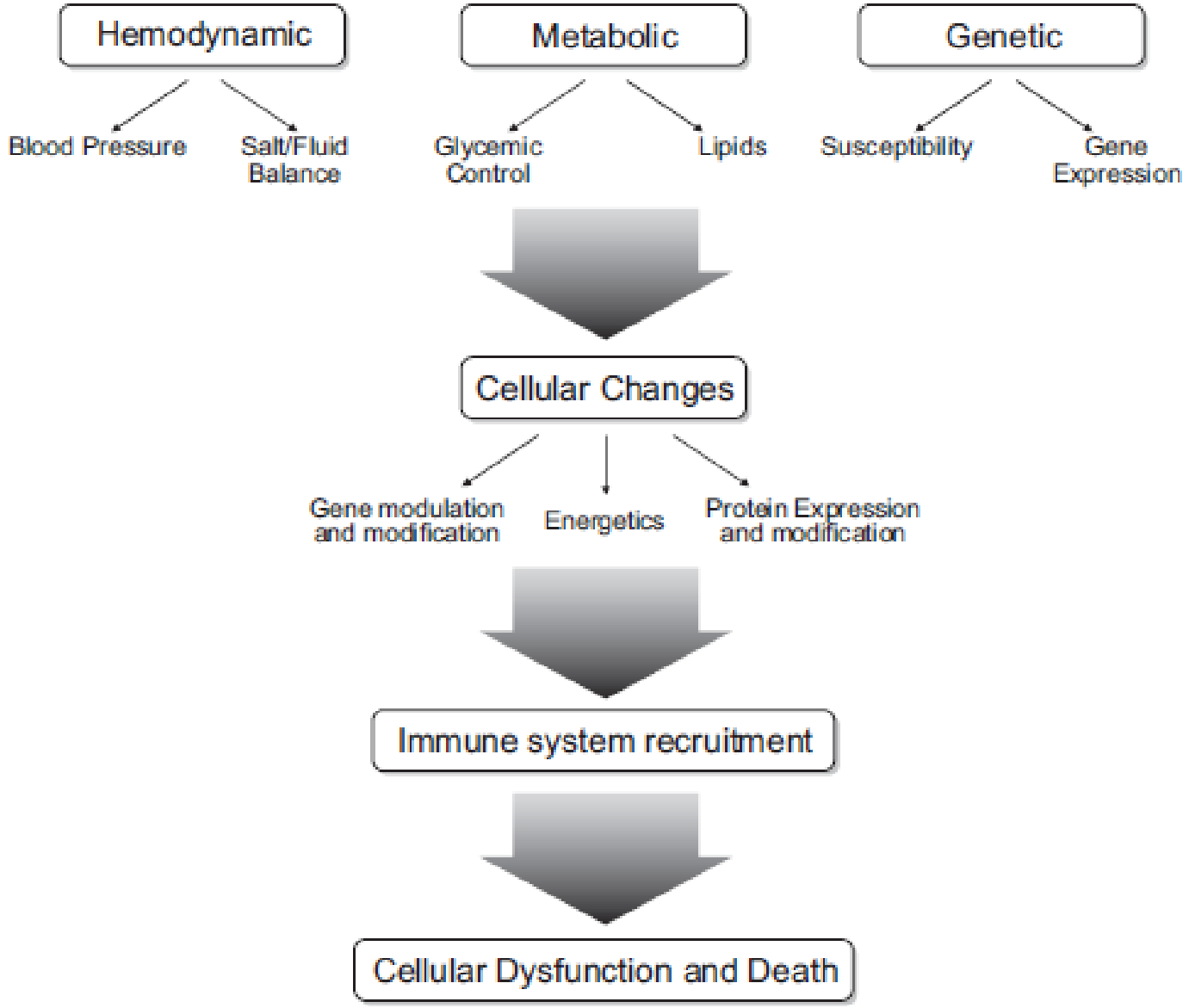



**FIGURE 1.** Schematic overview of the major areas contributing to diabetic complications.

# Long-term vascular complications

- **“microvascular disease” (due to damage to small blood vessels)**
  - **eye disease or “retinopathy”**
  - **kidney disease termed “nephropathy”**
  - **neural damage or “neuropathy”**
- **“macrovascular disease” (due to damage to the arteries)**
  - **accelerated cardiovascular disease (myocardial infarction)**
  - **cerebrovascular disease (strokes)**
- **Depression**
- **Dementia**
- **Sexual dysfunction**

# Risk of the major chronic complications in type 1 diabetes

- **Retinopathy (47%)**
- **Nephropathy (17%)**
- **Cardiovascular disease (14%)**

# Nephropathy

- **The major cause of endstage renal failure in Western societies**
- **proteinuria**
- **decline in glomerular filtration rate (GFR) – progresses over a long period of time, often over 10–20 years**
- **major risk factor for the development of macrovascular complications such as heart attacks and stroke**
- **Hypertension and poor glycemic control precede**
- **High blood pressure as a consequence**

# Nephropathy

- **High glucose**

**Cellular effects affecting**

- **resident kidney cells**
- **endothelial cells**
- **smooth muscle cells**
- **mesangial cells**
- **Podocytes**
- **cells of the tubular and collecting duct system**
- **inflammatory cells**
- **myofibroblasts**

# Nephropathy

- **Changes in hemodynamics - glomerular hyperfiltration**

- **Changes in the metabolic milieu**
- **release of vasoactive factors**
- **Alterations in signal transduction**
- **intrinsic defects in glomerular arterioles including electromechanical coupling**

- **Proteinuria - changes within glomerular epithelial cells (podocytes)**

# Nephropathy

- **Hypertrophy of the kidney**
- **Hyperfiltration**

  **Increased amounts of**
  - **Glucose**
  - **fatty acids**
  - **Proteins**
  - **amino acids,**
  - **growth factors**
  - **cytokines**

  - **energetic imbalances,**
  - **redox abnormalities,**
  - **fibrosis,**
  - **Inflammation**

***deposition of extracellular matrix in the tubular component of the kidney (tubulointerstitial fibrosis) – endstage renal disease***

# Nephropathy

- **Treatment**

- **target systemic blood pressure and/or intraglomerular hypertension**

- **angiotensin converting enzyme (ACE) inhibitors**
- **angiotensin II (ANG II) receptor antagonists**

# Retinopathy

- a spectrum of lesions within the retina
- the leading cause of blindness among adults aged 20–74 years

changes in

- vascular permeability
- capillary microaneurysms,
- capillary degeneration,
- excessive formation of new blood vessels (neovascularization)
- retinal electrophysiology

# Retinopathy

**Clinically**

**After 20 years with the disease**

- **Nonproliferative stage**
    - **changes in the integrity of blood vessels within the retina, altering the blood-retinal barrier and vascular permeability**
    - **No symptoms**
- **Proliferative stage**
    - **Neovascularization**
    - **accumulation of fluid within the retina (macula edema)**
    - **Visual impairment**
    - **Bleeding**
    - **distorting of the retinal architecture**
    - **retinal detachment**

# Retinopathy

**Treatment**

- **laser photocoagulation**
- **Injection of the steroid triamcinolone**
- **Vascular endothelial growth factor (VEGF) antagonists into the eye**
- **vitrectomy**

# Neuropathy

- More than half of all individuals

- risk of one or more lower extremity amputations

- Impaired function of the peripheral nervous system

- Impaired wound healing
- erectile dysfunction
- Cardiovascular dysfunction

- Hypoxia
- capillary basement membrane thickening
- endothelial hyperplasia

- loss of sensory perception
- Hyperalgesia
- paresthesias,
- Allodynia
- numbness, dysesthesia (pins and needles)
- nighttime pain

# Cardiovascular disease

- **risk of myocardial infarction equivalent to that of nondiabetic individuals who have previously had a myocardial infarction**
- **more than half of the mortality seen in the diabetic population**
- **threefold increased risk of myocardial infarction compared with the general population**
- **Premature atherosclerosis**
- **impaired cardiac function, predominantly diastolic dysfunction (exertional dyspnea)**
- **Stiffening of the myocardium due to cross-linking and extracellular matrix deposition, hypertrophy, and neuronal abnormalities**

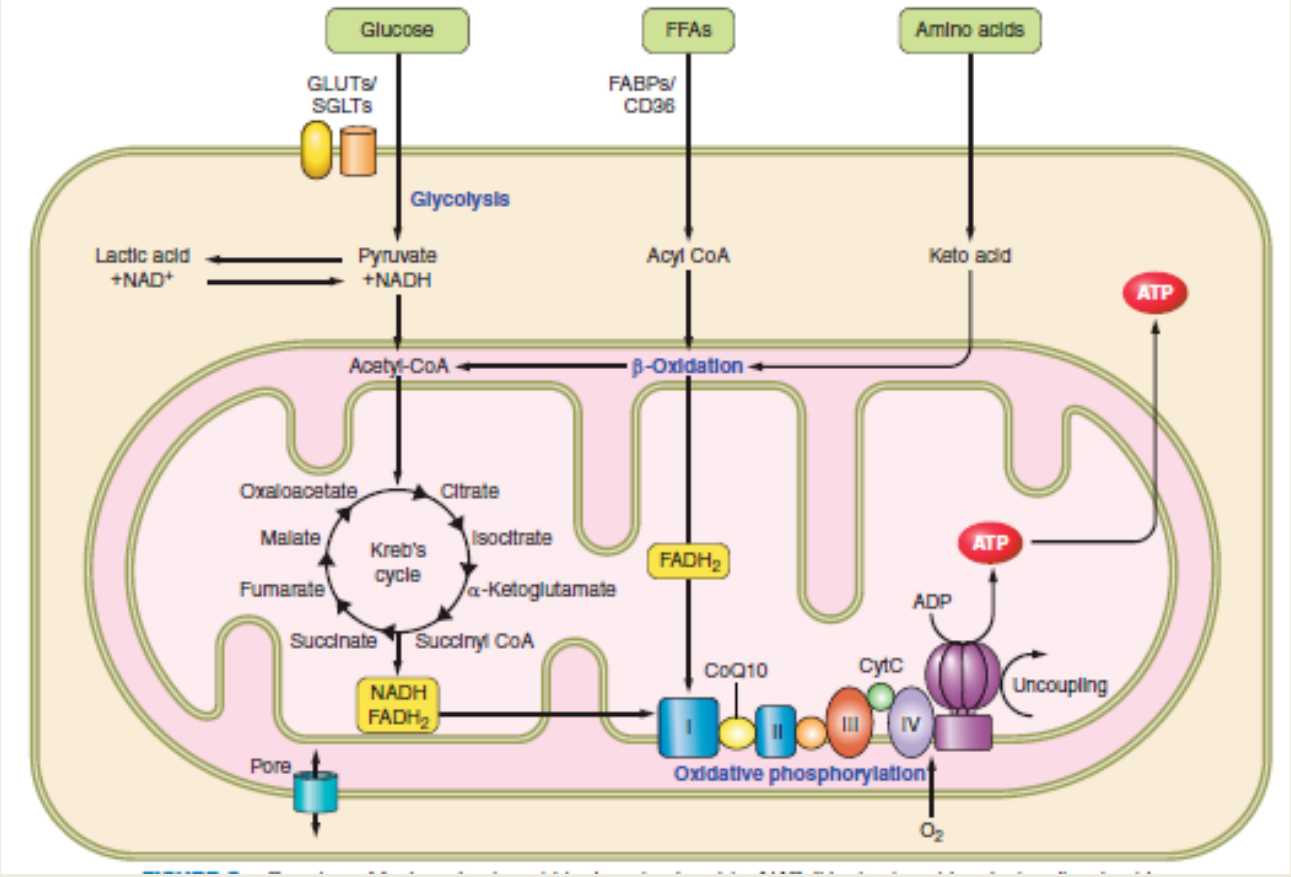
# Mechanisms of diabetic complications

- **Optimal glycemic control**
- **Losing control of energy production**
  - **Cells within tissues that are prone to diabetic complications, such as endothelial cells, are not able to modulate glucose transport rates to prevent excessive accumulation of intracellular glucose - energy production in these cells becomes uncontrolled**
  - **Abnormalities in energy production are thought to be major contributors to the development of diabetic complications**

# Mechanisms of diabetic complications

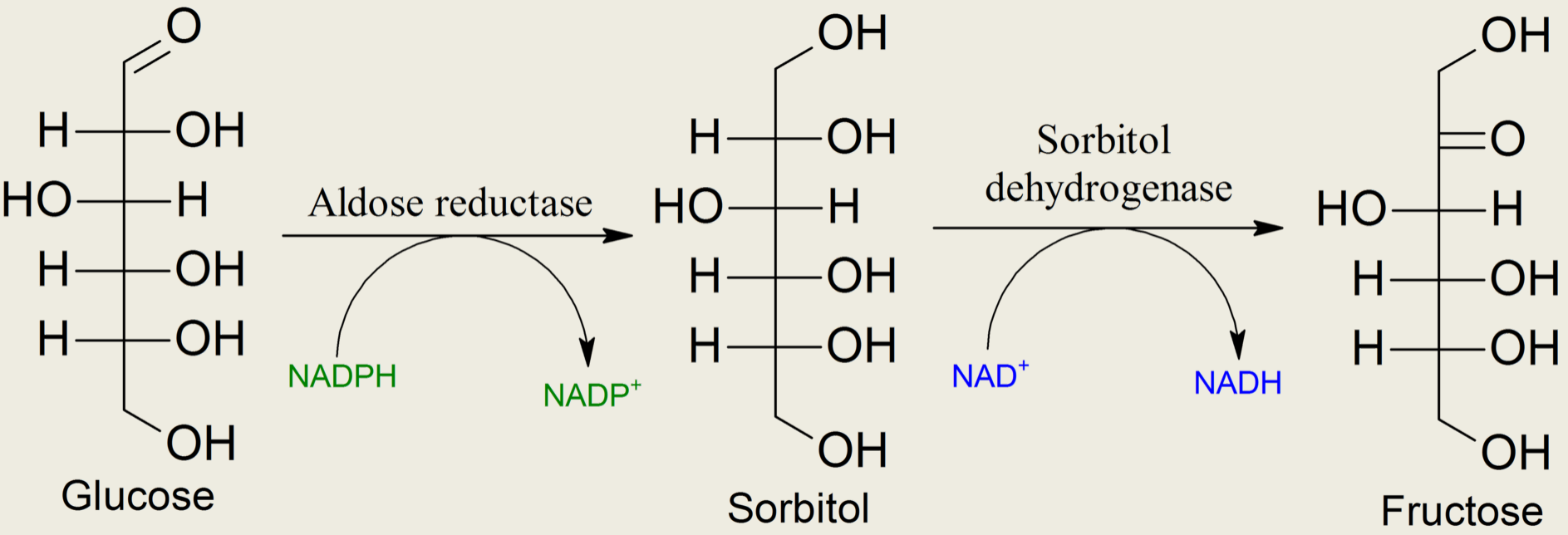
**Abnormalities in**

- **delivery of substrates**
- **switching the ratios of cell specific fuel sources among glucose intermediates, fatty acids and amino acids,**
- **changes in respiratory chain protein function,**
- **Uncoupling of the respiratory chain**



# Mechanisms of diabetic complications

## The sorbitol/polyol pathway



# Mechanisms of diabetic complications

## Insulin resistance

- **the loss of cellular signaling in response to the hormone insulin**

# Mechanisms of diabetic complications

## Blood Pressure and Hemodynamics

- **systemic and tissue-derived components of the renin-angiotensin-aldosterone system**

# Mechanisms of diabetic complications

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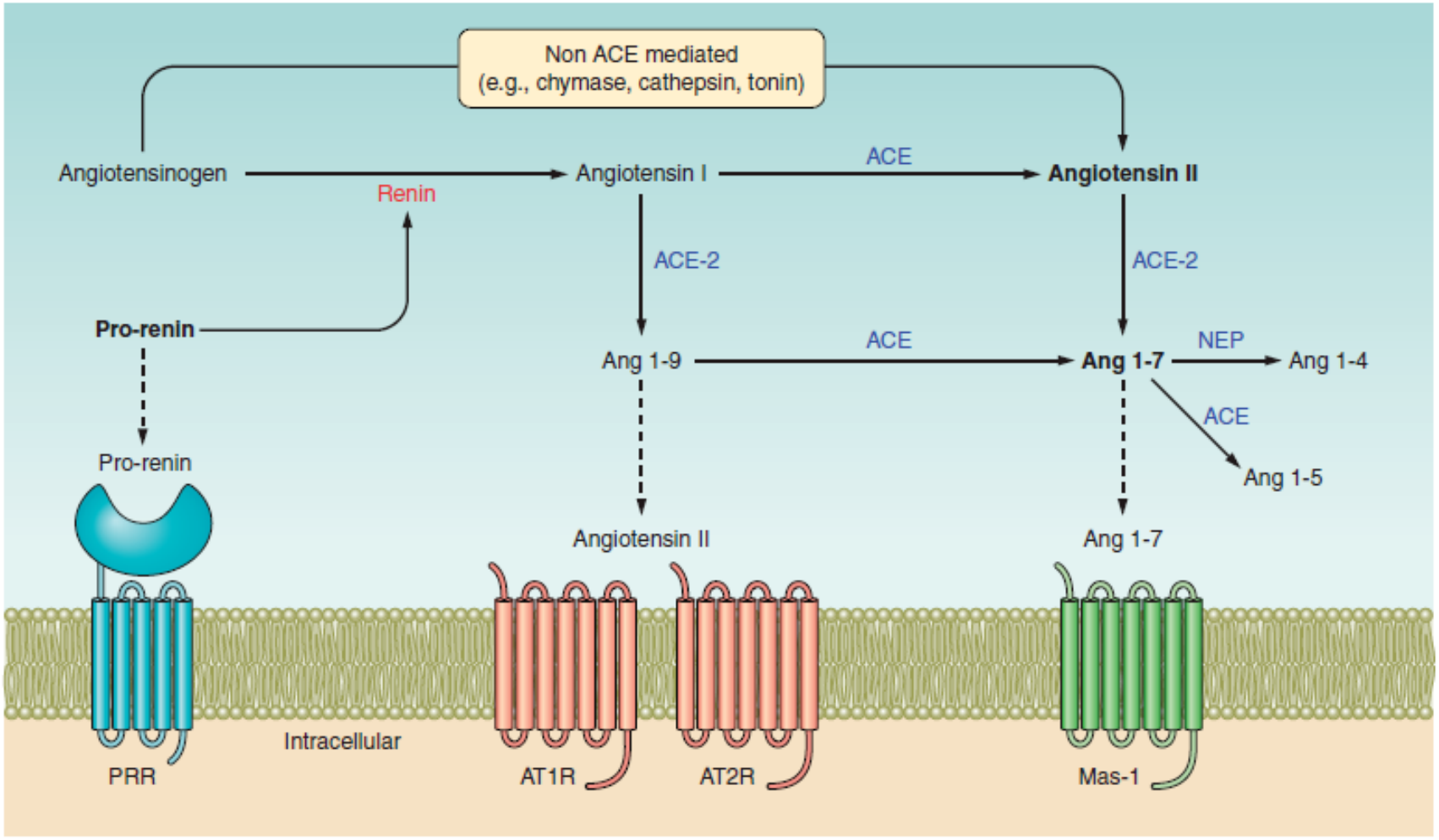
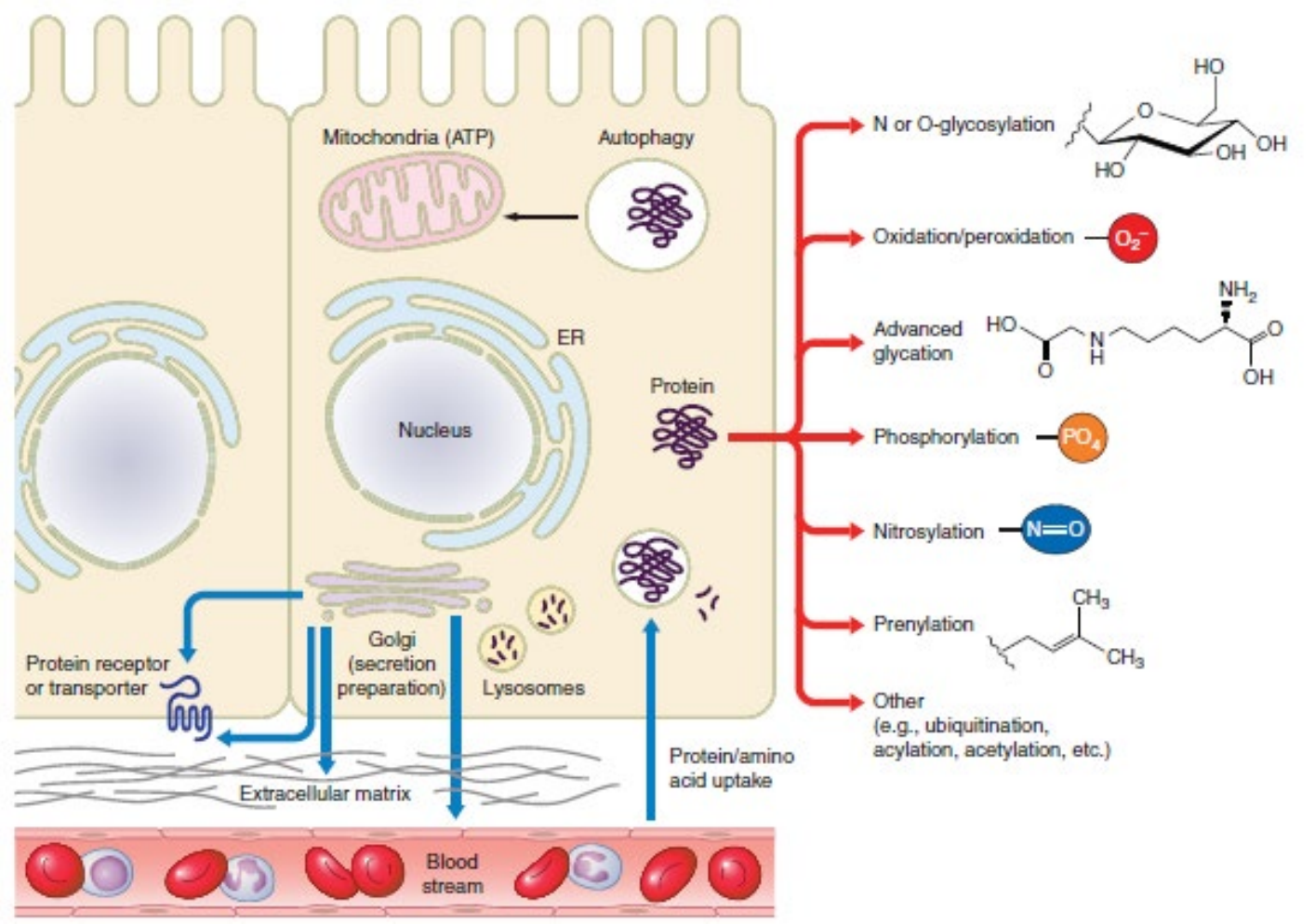


# Mechanisms of diabetic complications

- **Protein Modifications and Turnover**
  - **Protein folding**
  - **Autophagy**
  - **Posttranslational modifications**

# Mechanisms of diabetic complications

- **Posttranslational modifications**



# Mechanisms of diabetic complications

- **Advanced glycation end products**

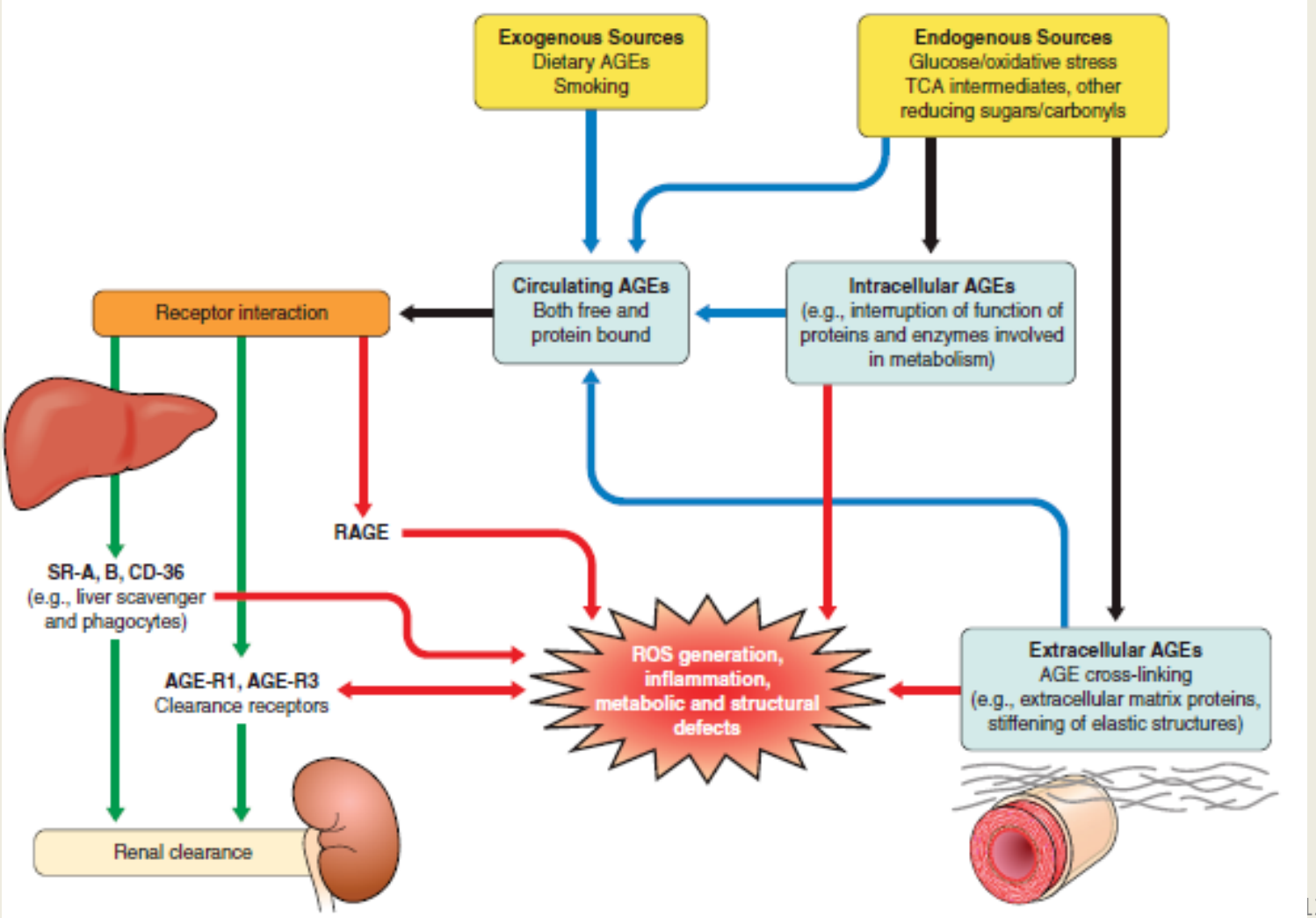


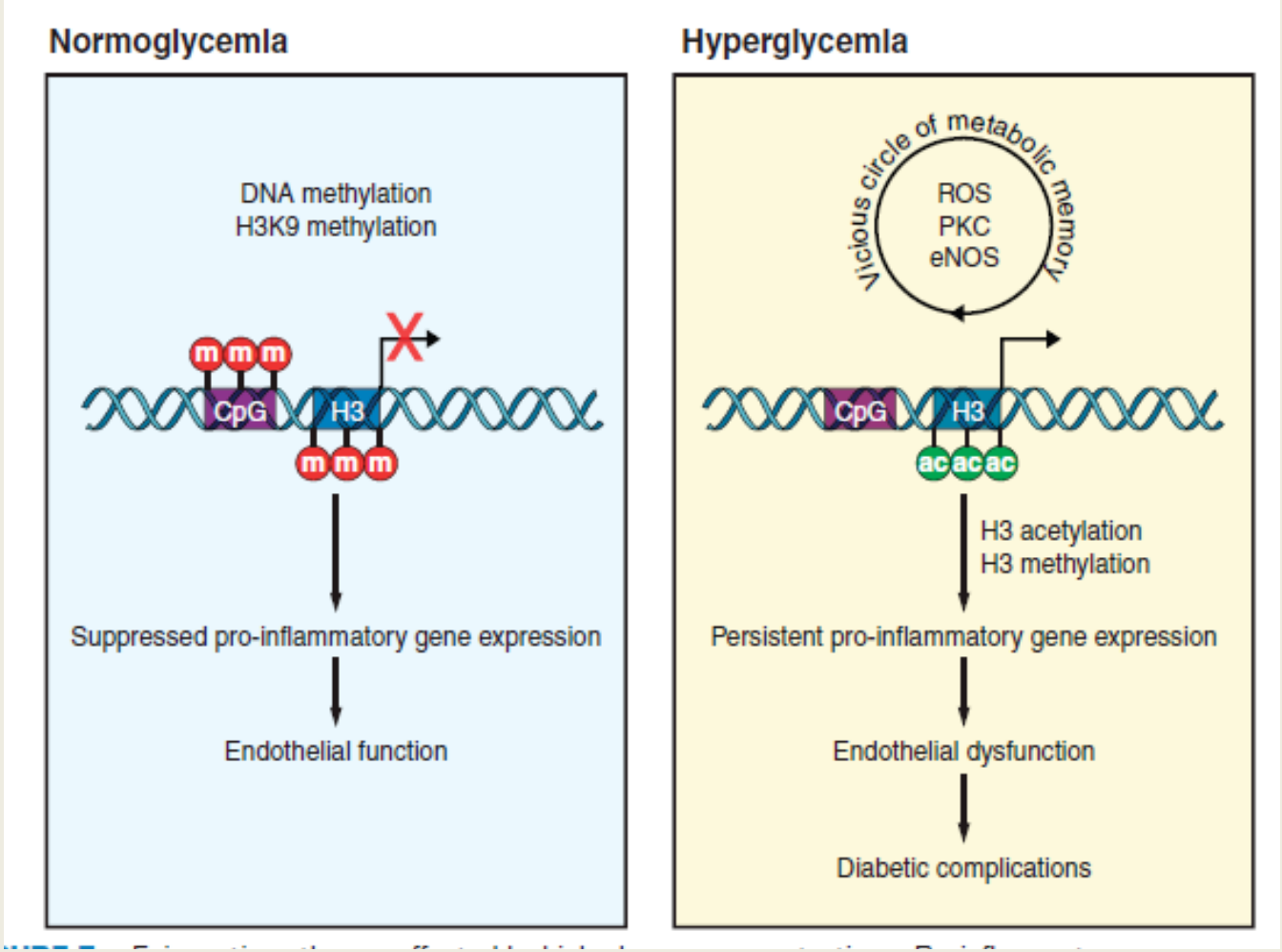

FIGURE 6. Advanced glycation end products and their trafficking. TCA, tricarboxylic acid cycle.

# Mechanisms of diabetic complications

- **Inflammation**
  - **Adhesion molecules**
  - **Leukocyte infiltration**
  - **Inflammatory cytokines**
  - **Growth factors**
  - **NF-κB**

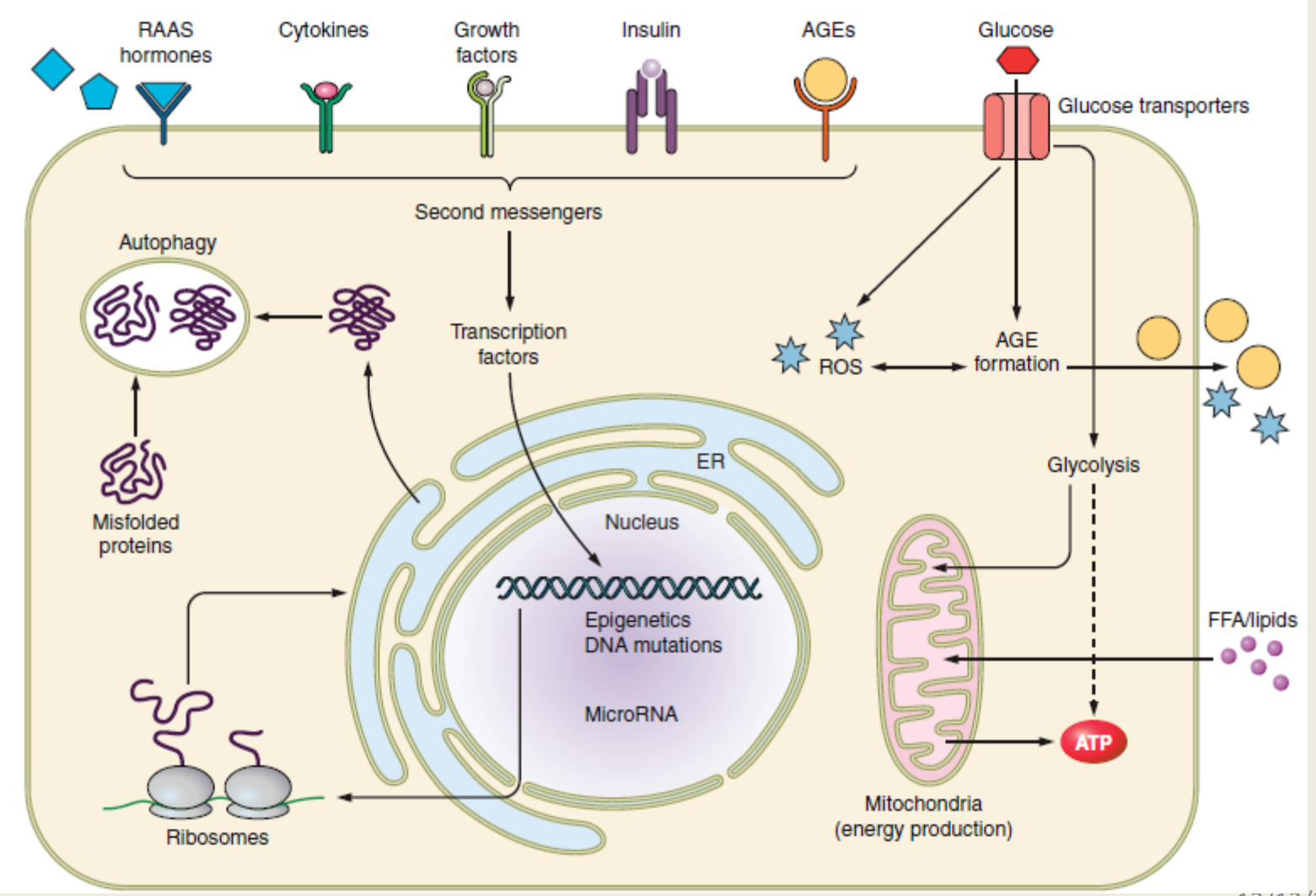
# Mechanisms of diabetic complications

- **Epigenetic gene regulation**



# Mechanisms of diabetic complications

- **Overview**



***Which sentence is incorrect?***

***1. Insulin promotes glycogen synthesis in the liver***

***2. Insulin promotes the synthesis of fatty acids in the liver***

***3. Insulin promotes gluconeogenesis in the liver***

***4. Insulin is secreted as a response to high blood glucose concentration***

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***1. Glucagon promotes the breakdown of glycogen in the liver***

***2. Glucagon inhibits glycolysis in the liver***

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***4. Glucagon promotes protein synthesis***

***5. Glucagon promotes the production of ketone bodies to be used as fuel in neurons***

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***Which sentence is incorrect? In the well-fed state***

***1. Amino-acids and glucose pass from the intestinal epithelial cells to the blood circulation and through the portal vein arrive to the liver.***

***2. Chylomicrons are secreted from intestinal epithelial cells to the lymphatic circulation towards body tissues***

***3. Glycogen synthesis is induced***

***4. Glycolysis is induced***

***5. Proteins are catabolized in skeletal muscles for glucose synthesis***

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***1. Cori and alanine cycles replace glucose breakdown in other tissues by glucose formation in the liver***

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***4. The brain completely oxidizes glucose***

***5. Branched-chain amino-acids (valine, leucine, isoleucine) provide nitrogen for alanine and glutamine in muscle cells***

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***Which of the following would favor gluconeogenesis in the fasted state?***

***1. Fructose 1,6-biphosphate stimulation of pyruvate kinase***

***2. Acetyl-CoA activation of pyruvate carboxylase***

***3. Citrate activation of acetyl-CoA carboxylase***

***4. Malonyl-CoA inhibition of carnitine palmitoyltransferase I***

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- **The increase in fatty acids in obesity leads to:**

- **A. Increased cellular glucose uptake through inactivation of PKC that activates transmembrane transport of GLUT transporters**

- **B. Decreased cellular glucose uptake through activation of PKC that inhibits translocation of GLUT transporters to the membrane**

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- **Mobilization of stored triacylglycerols occurs through:**
- **A. of glucagon/epinephrine which activates PKA**
- **B. of insulin that activates PKA**
- **C. by shifting the hormone-sensitive lipase that breaks down triglycerides**
- **D. A + C**
- **E. B + C**

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- **In diabetes mellitus, insulin deficiency:**
- **A. leads to an inability to use glucose**
- **B. leads to insufficient synthesis of fatty acids**
- **C. leads to increased fat oxidation**
- **D. leads to overproduction of ketones**
- **E. leads to weight loss**
- **F. all of the above**

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**Between meals or during prolonged fasting, the regulation of carbohydrate metabolism in hepatocytes takes place:**

A. **through the glucagon/cAMP/PKA/glycogen synthase axis, leading to a decrease in glycogen synthesis.**

B. **B. through the glucagon/cAMP/PKA/glycogen synthase axis, leading to an increase in glycogen synthesis.**

C. **C. through the glucagon/cAMP/PKA/glycogen phosphorylase axis, leading to increased glycogen breakdown.**

D. **D. through the glucagon/cAMP/PKA/PFK-1 axis, leading to a decrease in glycolysis.**

E. **A + B + C**

F. **A + C + D**

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**How is insulin secretion regulated by pancreatic β-cells?**

A. **through the uptake and catabolism of glucose in β-cells**

B. **B. through ATP-gated potassium channels**

C. **through an increase in intracellular calcium concentration**

D. **through the glucose transporters SGLT1 and GLUT5**

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**In obese individuals, the increased concentration of fatty acids favors insulin resistance mainly through:**

A. **reduction of glucose intake due to the inability of insulin to bind to its receptor.**

B. **reduction of glucose uptake due to allosteric inhibition of GLUT4 transporters by fatty acids.**

C. **reduction of glucose uptake due to allosteric inhibition of GLUT4 transporters by PKC.**

D. **reduction of glucose uptake due to inhibition of insulin receptor signaling by PKC and inability to move GLUT4 to the cell membrane.**

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**During periods of prolonged fasting:**

A. **Glycogen synthesis in the liver and muscles increases.**

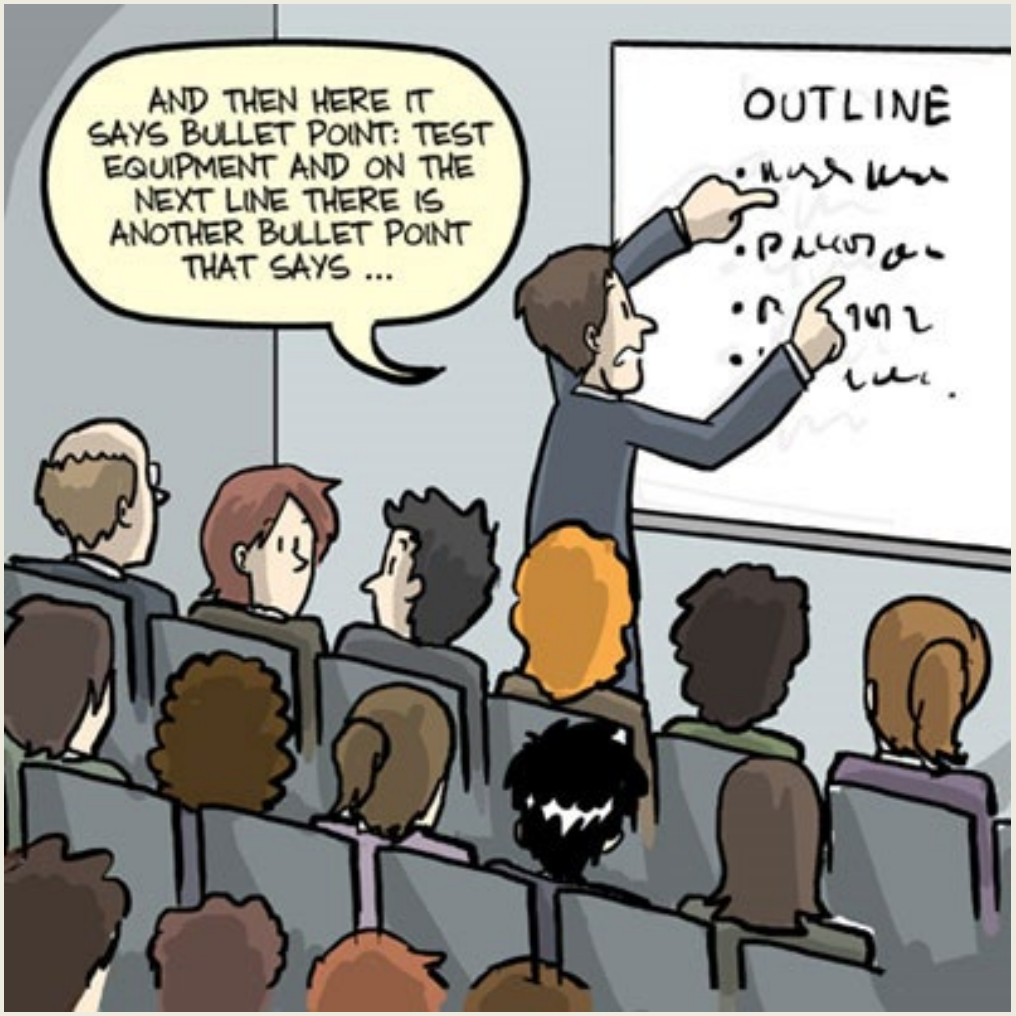
B. **The carbon skeleton of amino acids participates in gluconeogenesis and nitrogenous residues are eliminated in the form of urea.**

C. **Accumulation of acetyl-CoA favors entry into the citric acid cycle**

D. **Accumulation of acetyl-CoA favors the production of ketone bodies.**

E. **B + C**

F. **B + D**


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

Thank you!