Integration of metabolism

التكيف الأيضي Metabolic Adaptation

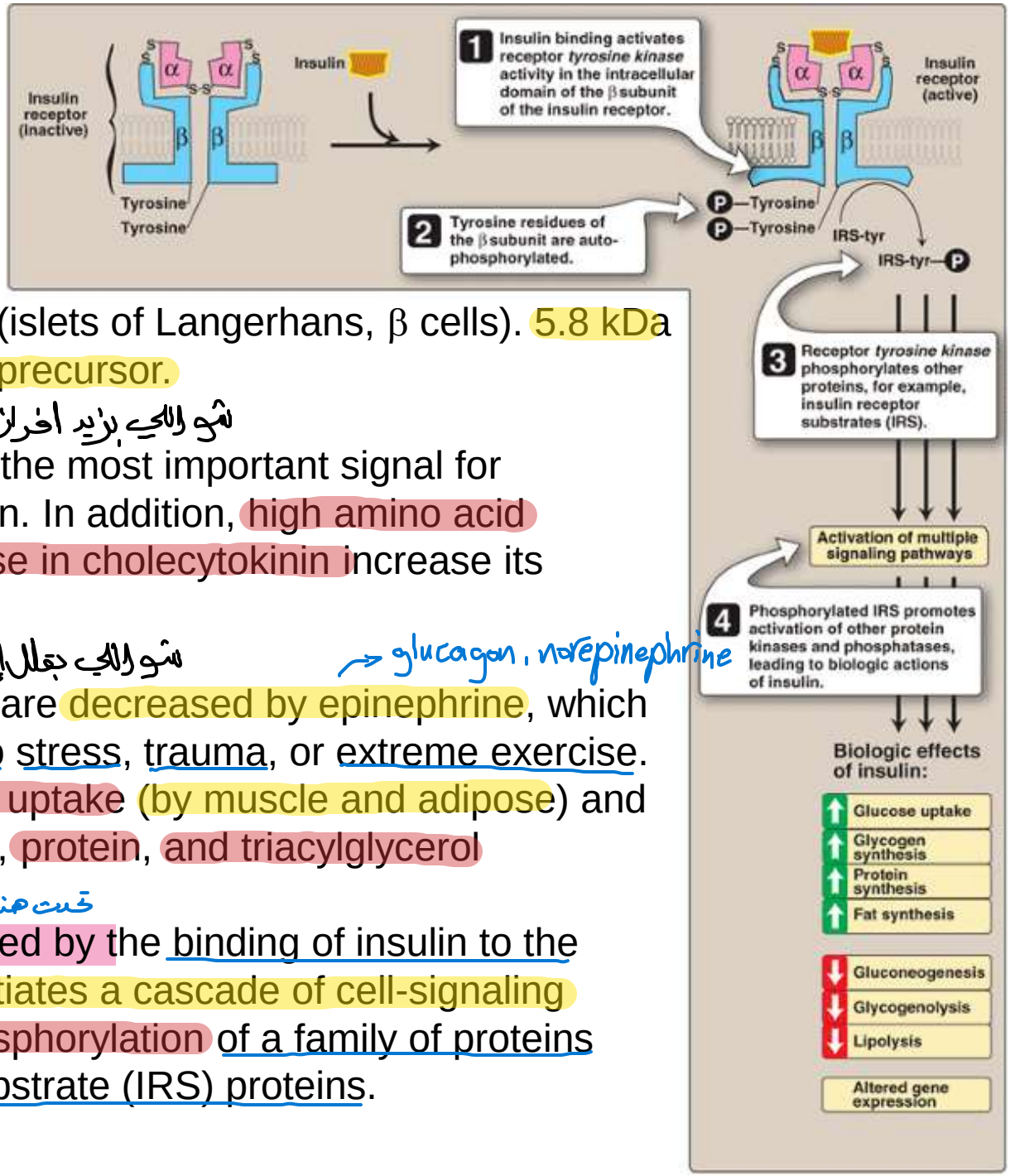
Fed State Blood glucose ~ 6 mM. Liver and muscle make glycogen. Liver uses amino acids and fatty acids. Triaclyglycerols stored in adipose cells.

6 -12 hrs Blood glucose ~ 4.5 mM. Liver uses muscle amino acids to make and export glucose. Triacylglycerols split and the glycerol is used by the liver to make glucose. Fatty acids used by liver and muscle.

1-3 days Carbohydrate reserves depleted (ينفذ). Muscle rapidly degraded to amino acids. Triacylglycerols used.

3 days Starvation مرحلة المجاعة Liver makes ketone bodies (Citric acid cycle slows). The switch to ketone body production is coordinated (تتزامن) with a decrease in the rate of protein degradation in muscle.

Insulin



- Synthesized in pancreas (islets of Langerhans, β cells). 5.8 kDa protein, cut from a larger precursor.

شو اللي بزيد افراز الإنسولين ؟!

- A rise in blood glucose is the most important signal for increased insulin secretion. In addition, high amino acid concentration and increase in cholecytokinin increase its secretion

شو اللي بقلل إفرازه ؟!

- Its synthesis and release are decreased by epinephrine, which is secreted in response to stress, trauma, or extreme exercise. Insulin increases glucose uptake (by muscle and adipose) and the synthesis of glycogen, protein, and triacylglycerol

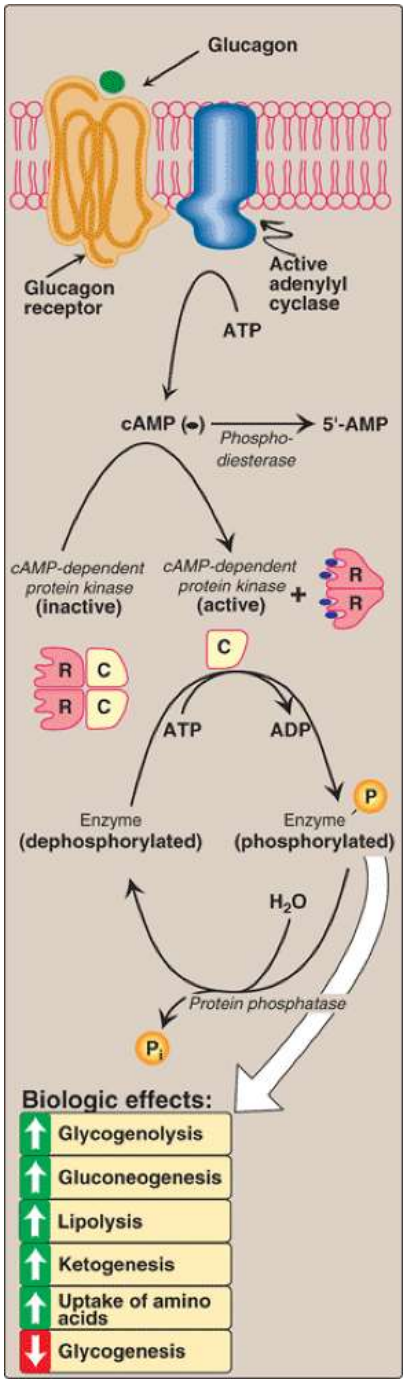
glucagon, norepinephrine

تمت هذه العمليات عن طريق

- These actions are mediated by the binding of insulin to the insulin receptor, which initiates a cascade of cell-signaling responses, including phosphorylation of a family of proteins called insulin receptor substrate (IRS) proteins.

Glucagon

- Glucagon is a polypeptide hormone secreted by the α cells of the pancreatic islets. Glucagon, along with epinephrine, cortisol, and growth hormone (the "counter-regulatory hormones"), opposes many of the actions of insulin. هذول الهرمونات شغلهم عكس شغل الانسولين
- Glucagon acts to maintain blood glucose during periods of potential hypoglycemia. Glucagon increases glycogenolysis, gluconeogenesis, lipolysis, ketogenesis, and uptake of amino acids.
- Glucagon secretion is stimulated by low blood glucose, amino acids, and epinephrine. Its secretion is inhibited by elevated blood glucose and by insulin.
- Glucagon binds to high-affinity receptors of hepatocytes. Primary target liver and adipose tissue.



Hypoglycemia → decrease the level of glucose in blood

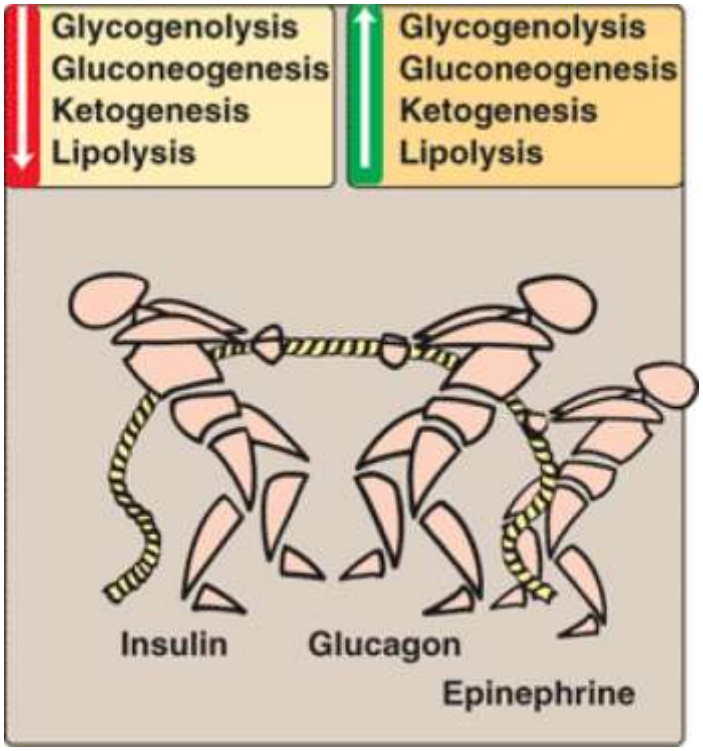
- Hypoglycemia is characterized by: ارتباك سلوك غير طبيعي
  - Central nervous system symptoms, including confusion, aberrant behavior, or coma
  - A simultaneous blood glucose level equal to or less than 40 mg/dl
  - Resolution of these symptoms within minutes following the administration of glucose. ↘ تختفي إعطاء

- Hypoglycemia most commonly occurs in patients receiving insulin treatment with tight control. ← رقابة شديدة

- The consumption and subsequent عمليات metabolism of **ethanol** inhibits gluconeogenesis, leading to hypoglycemia in individuals with depleted stores of liver glycogen. Alcohol consumption can also increase the risk for hypoglycemia in patients using insulin. نفاذ

Epinephrine

- Epinephrine is a Catecholamine, When released from presynaptic nerve endings, serves as neurotransmitter.
- When released from adrenal medulla, acts as hormone. Signals glucose limitation.
- Main targets muscle and adipose tissue.
- Inhibits insulin secretion and stimulates glucagon secretion.
- Part of “flight or fight” response.



Major hormones controlling fuel metabolism in mammals

Insulin	**Glucagon**	**Epinephrine**
stimulates		
glucose uptake	**cAMP**	**cAMP**
glycolysis → تحلل الجلوكوز	**glycogenolysis**	**triacylglycerol hydrolysis**
glycogenesis → تكوين جلايكوجين	**gluconeogenesis**	**glycogenolysis**
triacylglycerol synthesis	**triacylglycerol hydrolysis**	لـ تحلل جلايكوجين
protein, DNA, RNA synthesis	لـ تحلل مائي	
Inhibits		
Gluconeogenesis → تكوين جلوكوز	glycogenesis	glycogenesis
lipolysis	glycolysis	
protein degradation		

Enzymatic changes in the fed state

توفر الجلوكوز يحفز الانزيمات خلال الجلوكوز (بعد الأكل)

- Availability of the substrate
- Allosteric effect
  - For example, glycolysis in liver is stimulated after meal by elevation in fructose 2,6-bisphosphate which is an allosteric activator of phosphofructokinase-1
- Regulation of enzymes by covalent modification
  - In the fed state, most of the enzymes regulated by covalent modification are in the dephosphorylated form and are active (exceptions: are glycogen phosphorylase, fructose 2,6-bisphosphatase-2, and hormone-sensitive lipase of adipose tissue, which are inactive in their dephosphorylated state).

هاي الإنزيمات بتكون نشطة بحالة الفسفرة

- Induction and repression of enzyme synthesis → تحفيز/كبح
  - For example, in the fed state, elevated insulin levels result in an increase in the synthesis of key enzymes involved in anabolic metabolism

لعمليات البناء

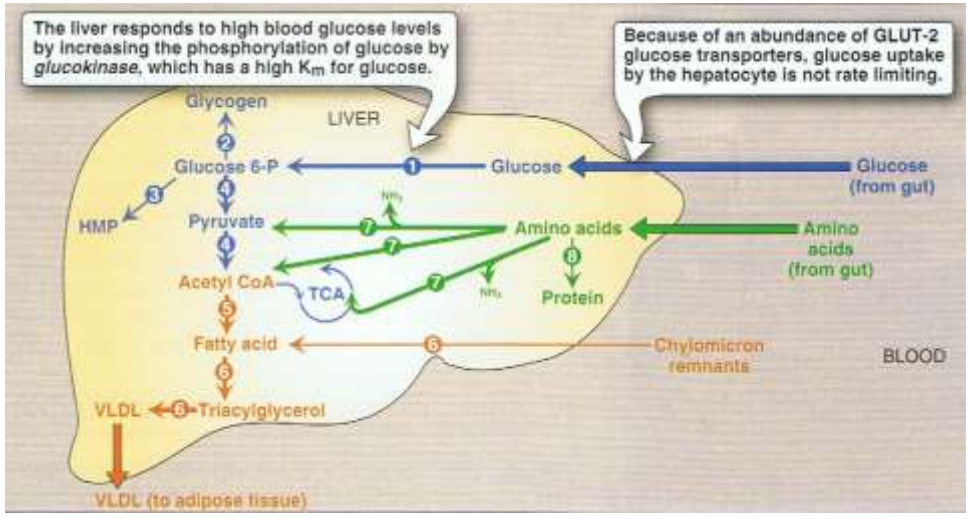
In fed state

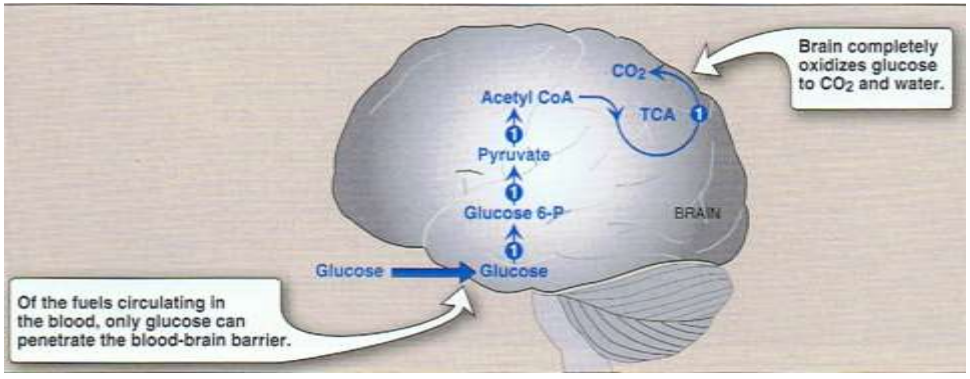
- After ingestion of the meal, absorptive state took 2-4 hr where an increase in glucose, amino acids and TAG in blood is observed
- As a response pancreas will increase the secretion of insulin and drop the release of glucagon by islets of langerhans
- During the absorptive state, all tissues use glucose as a feul

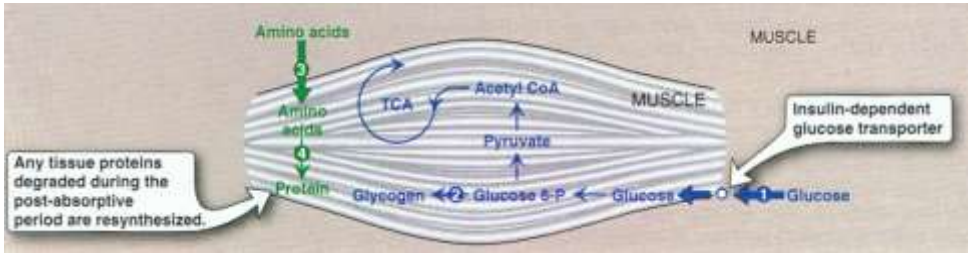
In fed state

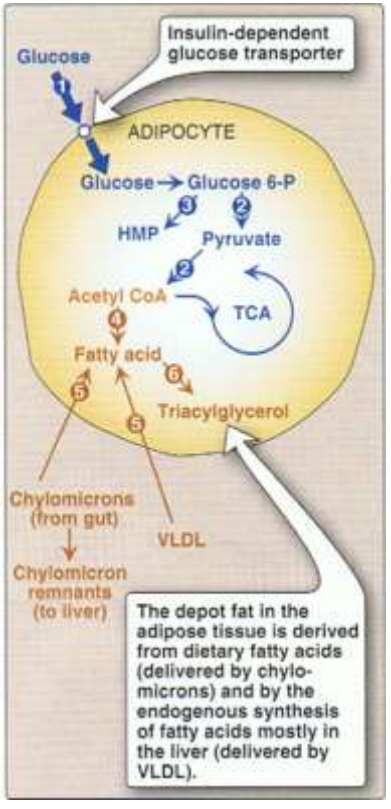
- In liver:
  - It starts glycogenesis to replinish glycogen store.
  - Replaces any needed hepatic proteins
  - Increase TAG synthesis, which are packaged as very low density lipoprotein (VLDL) and exported to the perepheral tissue
- In resting skeletal muscles
  - Increase protein synthesis to replace protein degraded since the previous meal
- In adipose tissue
  - Increase the TAG synthesis and storage
- In brain
  - It uses glucose extensively as feul

In fed state


The liver responds to high blood glucose levels by increasing the phosphorylation of glucose by glucokinase, which has a high K_m for glucose.
Because of an abundance of GLUT-2 glucose transporters, glucose uptake by the hepatocyte is not rate limiting.
Glycogen
LIVER
Glucose 6-P
Glucose
Glucose (from gut)
HMP
Pyruvate
Amino acids
Amino acids (from gut)
Acetyl CoA
TCA
Protein
Fatty acid
Chylomicron remnants
BLOOD
VLDL
Triacylglycerol
VLDL (to adipose tissue)


Brain completely oxidizes glucose to CO_2 and water.
CO_2
Acetyl CoA
TCA
Pyruvate
Glucose 6-P
BRAIN
Glucose
Glucose
Of the fuels circulating in the blood, only glucose can penetrate the blood-brain barrier.


Amino acids
MUSCLE
Amino acids
TCA
Acetyl CoA
MUSCLE
Pyruvate
Insulin-dependent glucose transporter
Any tissue proteins degraded during the post-absorptive period are resynthesized.
Protein
Glycogen
Glucose 6-P
Glucose
Glucose


Glucose
Insulin-dependent glucose transporter
ADIPOCYTE
Glucose
Glucose 6-P
HMP
Pyruvate
Acetyl CoA
TCA
Fatty acid
Triacylglycerol
Chylomicrons (from gut)
VLDL
Chylomicron remnants (to liver)
The depot fat in the adipose tissue is derived from dietary fatty acids (delivered by chylo-microns) and by the endogenous synthesis of fatty acids mostly in the liver (delivered by VLDL).

In fast state (starvation)

- Decrease in blood glucose, aa, and TAG levels leading to decrease in insulin secretion and increase in glucagon and epinephrine release

- For the liver, adipose, skeletal muscles, and brain, their are two priorities:
  - Need to maintain adequate plasma level of glucose to sustain energy metabolism of the brain and other glucose-requiring tissues such as RBCs
  - Need to mobilize fatty acids from adipose tissue and ketone bodies from liver to to supply energy to the other tissues

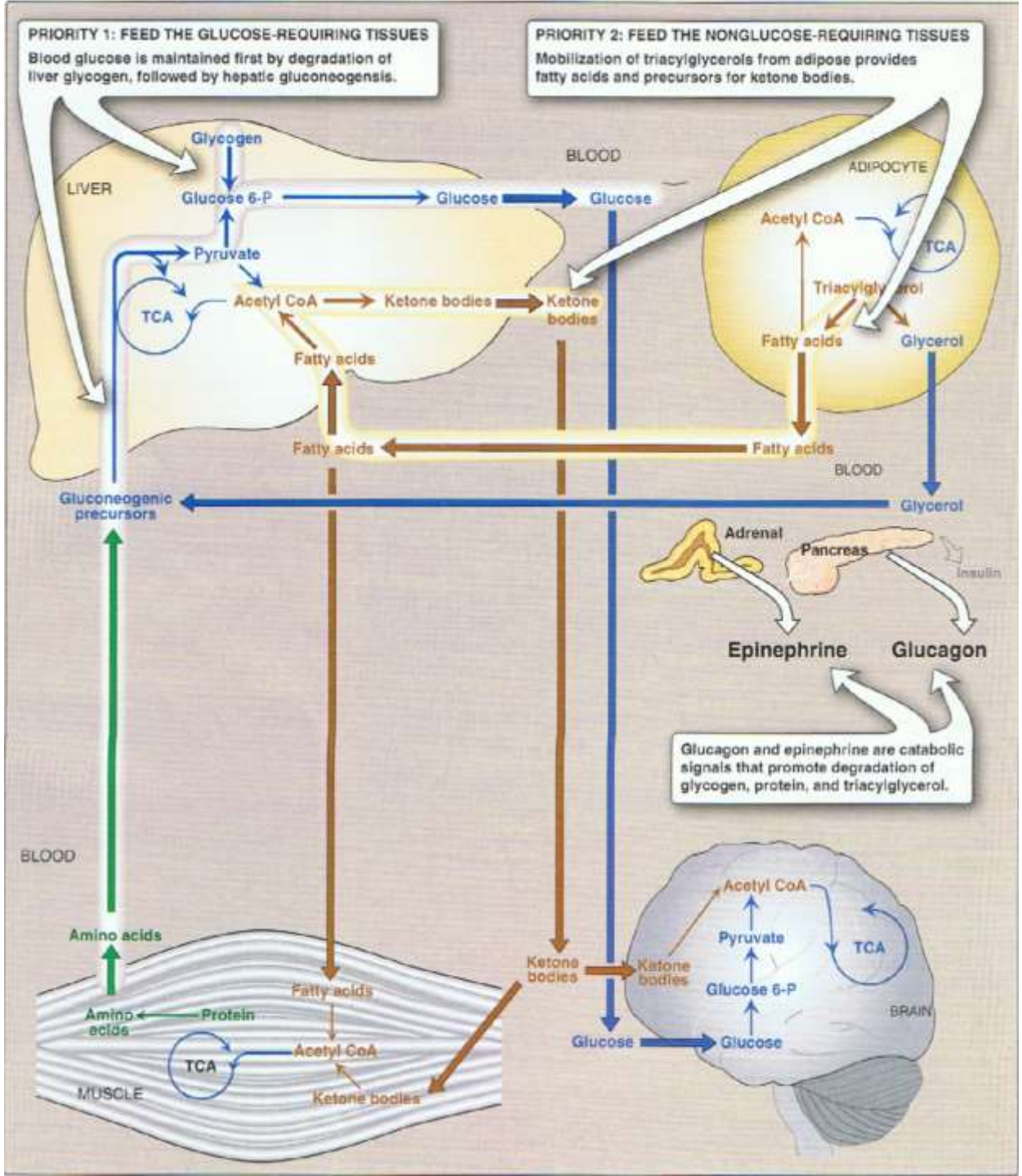
In fast state (starvation)

- In liver, this is accomplished by:
  - Glycogenolysis
  - Initiate gluconeogenesis using both increased fatty acid oxidation as source energy and supply acetyl coA for synthesis of ketone bodies

- Adipose tissues: will degrade stored TAG to fatty acids and glycerol that move to the liver → oxidation for fatty acid as a source of energy

- Muscles:
  - start using fatty acids and ketone bodies as feul
  - Muscle proteins are degraded to supply amino acids for the liver to use in gluconeogenesis → تصنيع للغلوكوز

- Brain can use glucose (short fasting) and ketone bodies (long fasting) as feul


PRIORITY 1: FEED THE GLUCOSE-REQUIRING TISSUES
Blood glucose is maintained first by degradation of liver glycogen, followed by hepatic gluconeogensis.
PRIORITY 2: FEED THE NONGLUCOSE-REQUIRING TISSUES
Mobilization of triacylglycerols from adipose provides fatty acids and precursors for ketone bodies.
Glycogen
LIVER
Glucose 6-P
Glucose
BLOOD
Glucose
ADIPOCYTE
Acetyl CoA
TCA
Pyruvate
Acetyl CoA
Ketone bodies
Ketone bodies
TCA
Fatty acids
Fatty acids
Glycerol
Fatty acids
Fatty acids
BLOOD
Gluconeogenic precursors
Glycerol
Adrenal
Pancreas
Insulin
Epinephrine
Glucagon
Glucagon and epinephrine are catabolic signals that promote degradation of glycogen, protein, and triacylglycerol.
BLOOD
Amino acids
Acetyl CoA
Pyruvate
TCA
Ketone bodies
Ketone bodies
Glucose 6-P
Fatty acids
Amino acids
Protein
BRAIN
Glucose
Glucose
TCA
Acetyl CoA
MUSCLE
Ketone bodies

Diabetes mellitus (DM)

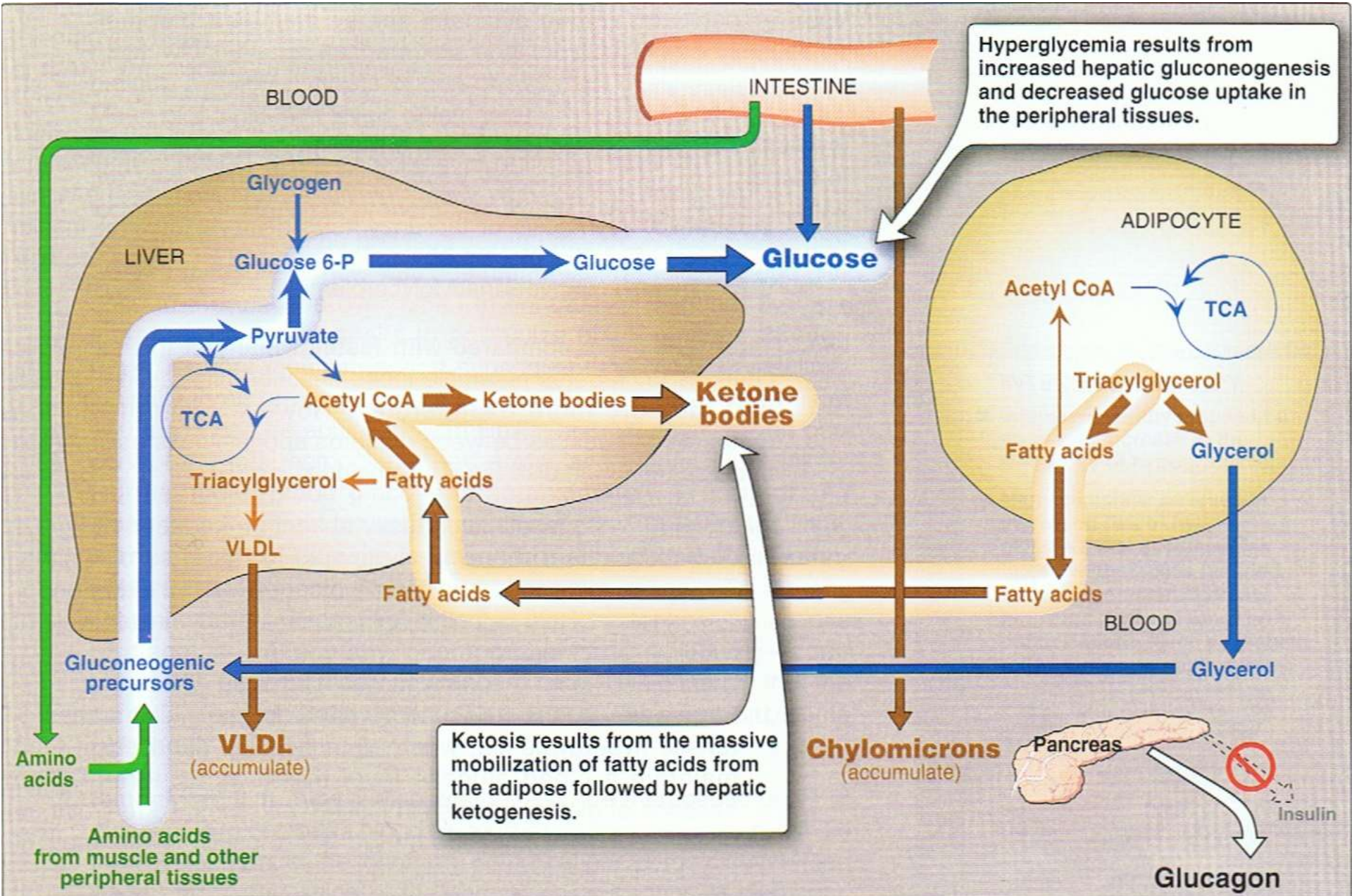
- A disease characterized by elevation of fasting blood glucose caused by relative or absolute deficiency of insulin

- The leading cause of adult blindness, renal failure, heart attacks and strokes.

- Can be of two types:
  - Type 1 DM: insulin dependent DM, usually during childhood, autoimmune, stimulated by environmental (viral) or genetic (low)
  - Type 2 DM: non insulin dependent DM, old people, genetic reasons mainly.

Type 1 diabetes mellitus (DM)

- Hyperglycemia and ketoacidosis
  - ↳elevation of glucose
  - ↳elevation of Ketone body
- Type 1 DM compared to fasting
  - Insulin level
  - Blood glucose level
  - Ketosis
  - hypertriacylgycerolemia

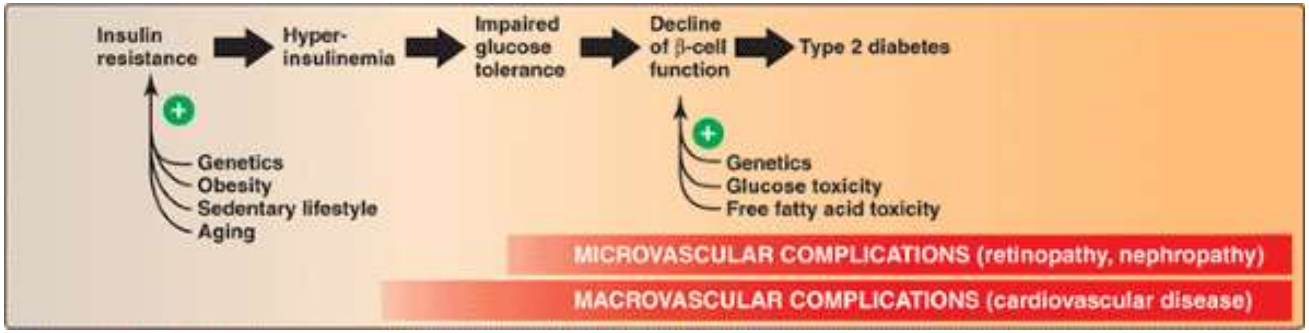

Hyperglycemia results from increased hepatic gluconeogenesis and decreased glucose uptake in the peripheral tissues.
BLOOD
INTESTINE
Glycogen
LIVER
Glucose 6-P
Glucose
Glucose
ADIPOCYTE
Acetyl CoA
TCA
Pyruvate
TCA
Acetyl CoA
Ketone bodies
Ketone bodies
Triacylglycerol
Fatty acids
Glycerol
Triacylglycerol
Fatty acids
VLDL
Fatty acids
Fatty acids
BLOOD
Gluconeogenic precursors
Glycerol
Amino acids
VLDL
(accumulate)
Ketosis results from the massive mobilization of fatty acids from the adipose followed by hepatic ketogenesis.
Chylomicrons
(accumulate)
Pancreas
Insulin
Amino acids from muscle and other peripheral tissues
Glucagon

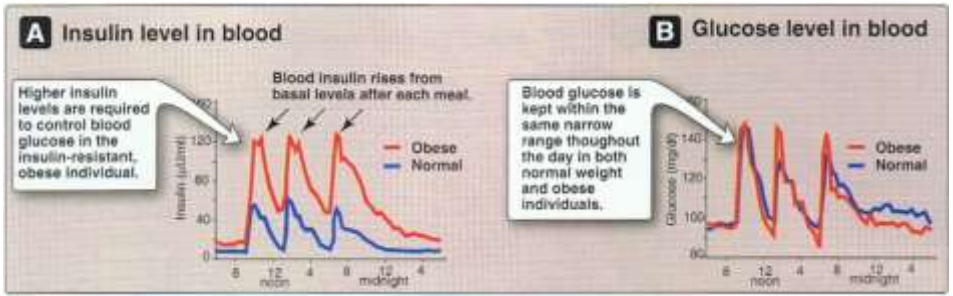
Type 2 diabetes mellitus (DM)

- Insulin resistance alone will not lead to Type 2 diabetes. But it develops in insulin-resistant individuals who show impaired β-cell function.

أسباب النوع الثاني من السكري؟!

- Insulin resistance and subsequent risk for the development of Type 2 diabetes is commonly observed in the **elderly**, and in individuals who are **obese**, **physically inactive**, or in the 3–5% of **pregnant women** who develop gestational diabetes.





Type 2 diabetes mellitus (DM)