ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

CARBOHYDRATE METABOLISM – OVERVIEW OF CARBOHYDRATE METABOLISM

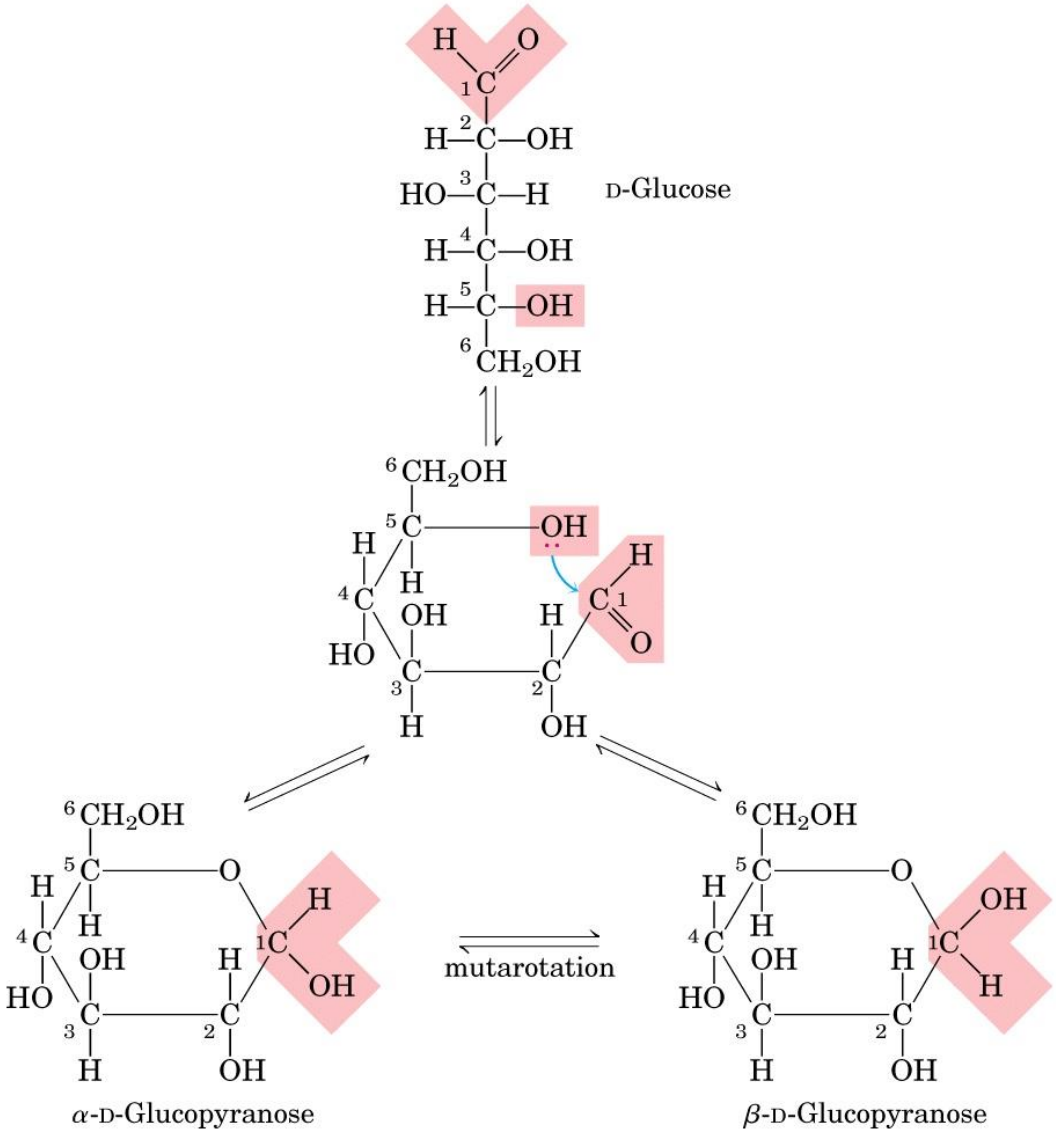
Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e Neuromotorie – DIBINEM – via Irnerio 48, Bologna

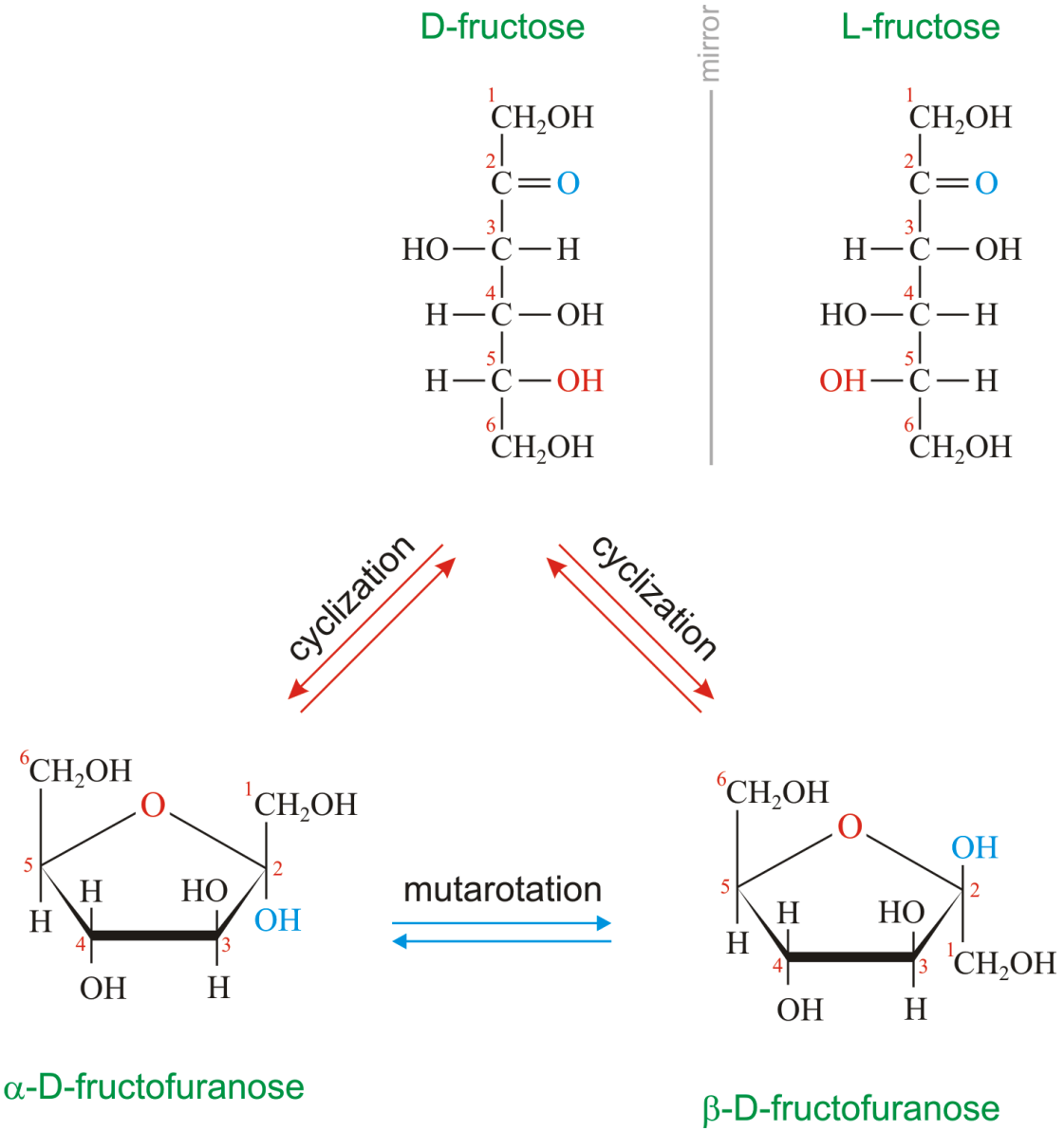
CARBOHYDRATE METABOLISM

- *Digestion and absorption*
- *General scheme: role of liver and extra-hepatic tissues*
- *Glycogen synthesis and breakdown*
- *Glycolysis*
- *Pyruvate oxidation*
- *Tricarboxylic Acid (TCA) Cycle*
- *Gluconeogenesis*
- *Pentose phosphate shunt*

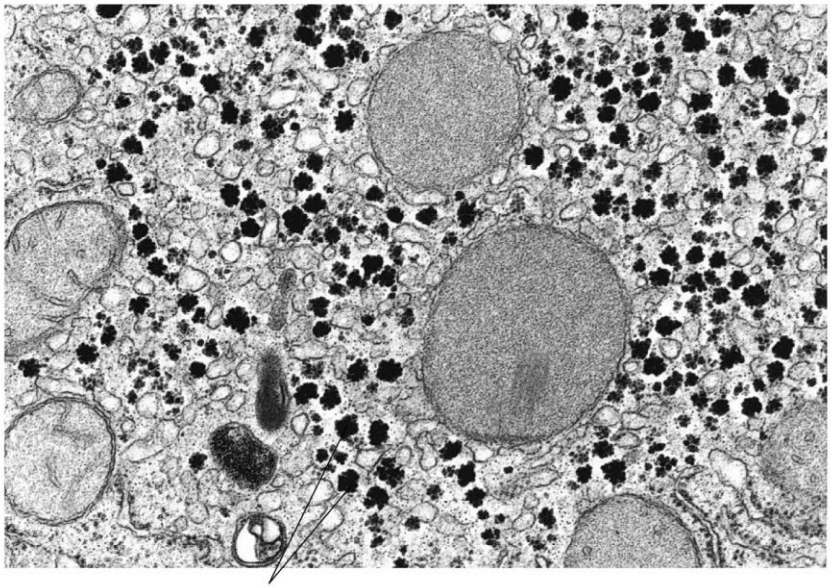
GLUCOSE



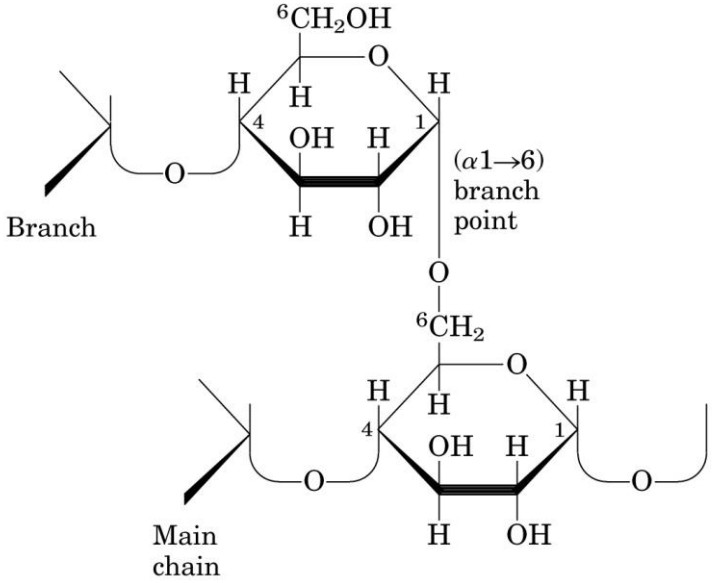
FRUCTOSE



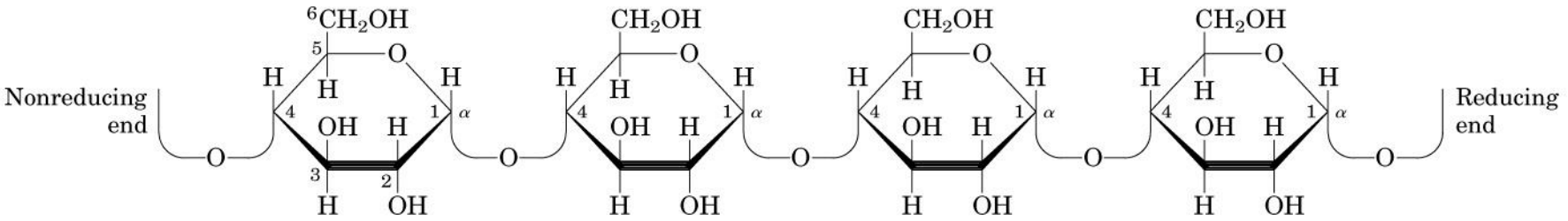
GLYCOGEN



(b)

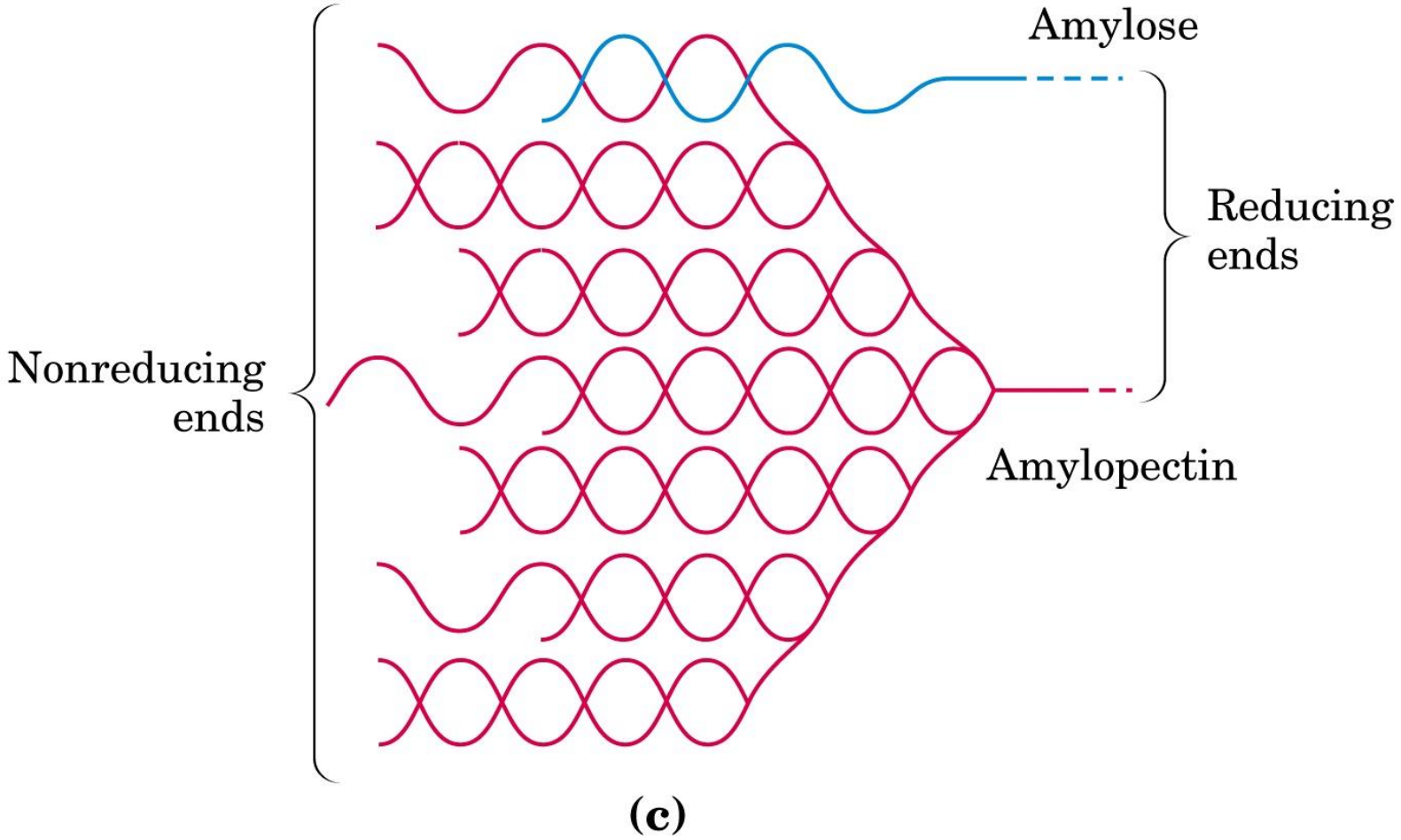


(b)

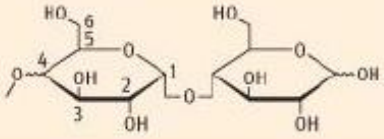
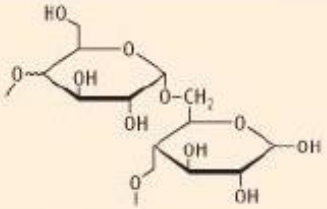
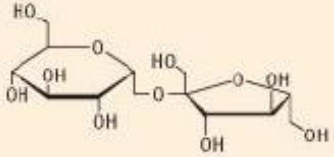
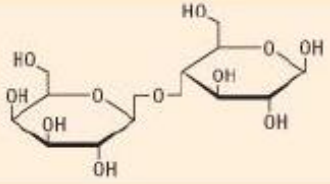
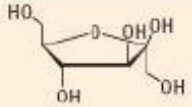
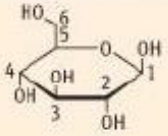


(a)

STARCH



OTHER CARBOHYDRATES

Carbohydrate	Food source	Structure
starch (amylose) [plant]	potatoes, rice, bread, onions	
amylopectin (glycogen) [plant, animal]	potatoes, rice, bread, muscle, liver	
sucrose	desserts, sweets, 'sugar'	
lactose	milk	
fructose	fruits, honey	
glucose	fruits, honey	

DIGESTION AND INTESTINAL ABSORPTION

Major **carbohydrates** in food:

- Polysaccharides:

  starch → glucose

- Disaccharides:

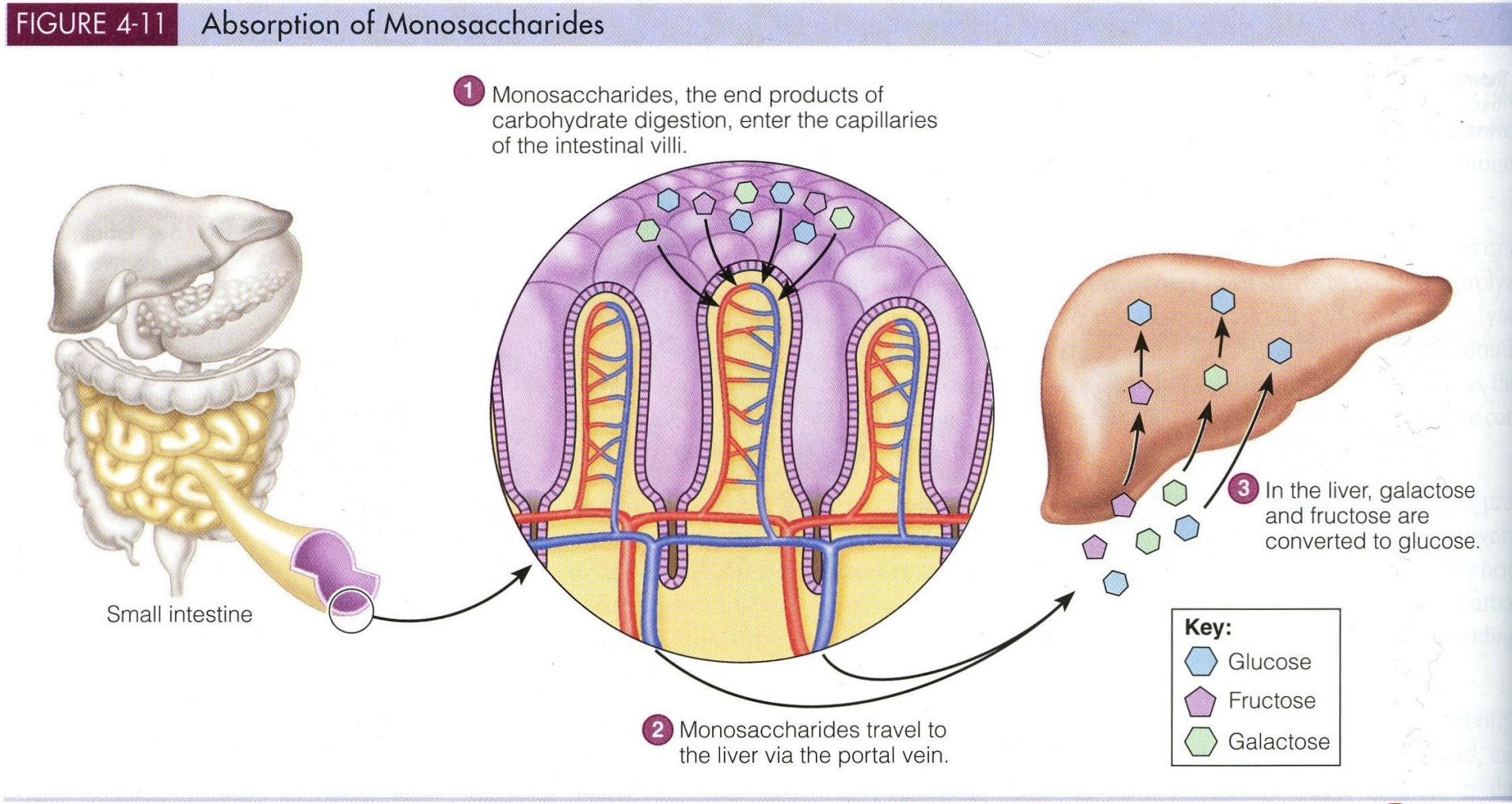
  lactose → galactose + glucose

  sucrose → fructose + glucose

Digestion: amylases from saliva and pancreas

Absorption: through intestinal microvilli by secondary active transport

GLUCOSE ABSORPTION

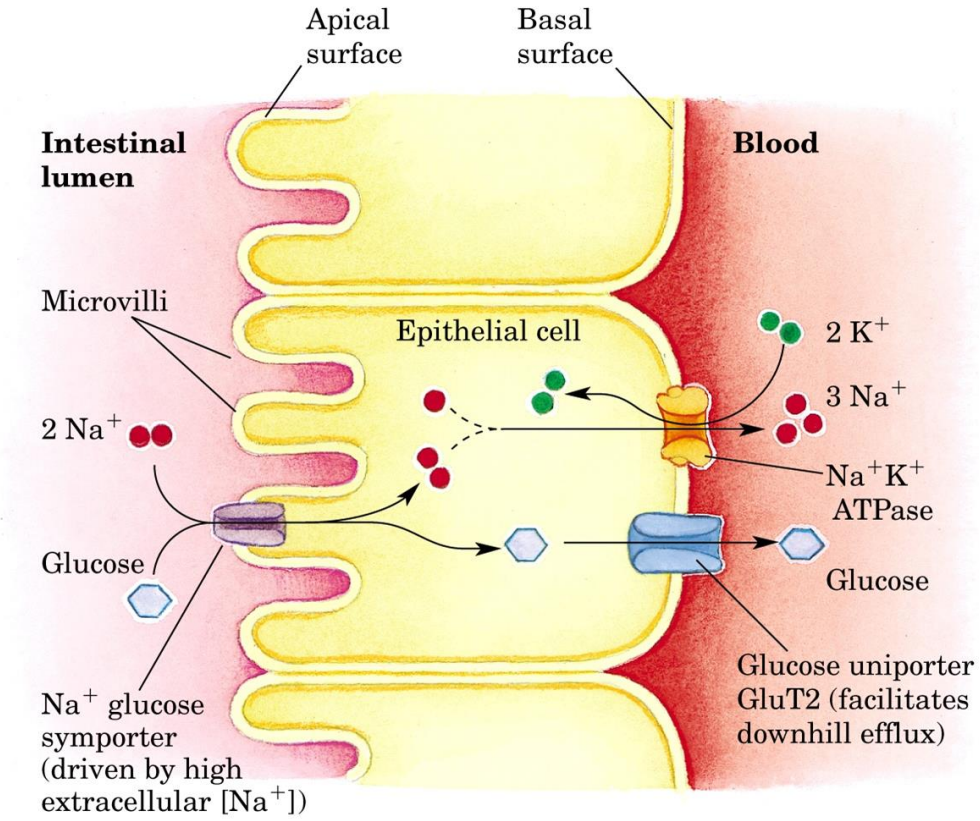


GLUCOSE ABSORPTION

$[Glucose]_{out} \rightarrow [Glucose]_{in}$ $\Delta G > 0$

$[Na^+]_{out} \rightarrow [Na^+]_{in}$ $\Delta G << 0$

Co-transport Glucose + 2 Na^+ $\Delta G < 0$



Primary active transport

Passive transport

Secondary active transport

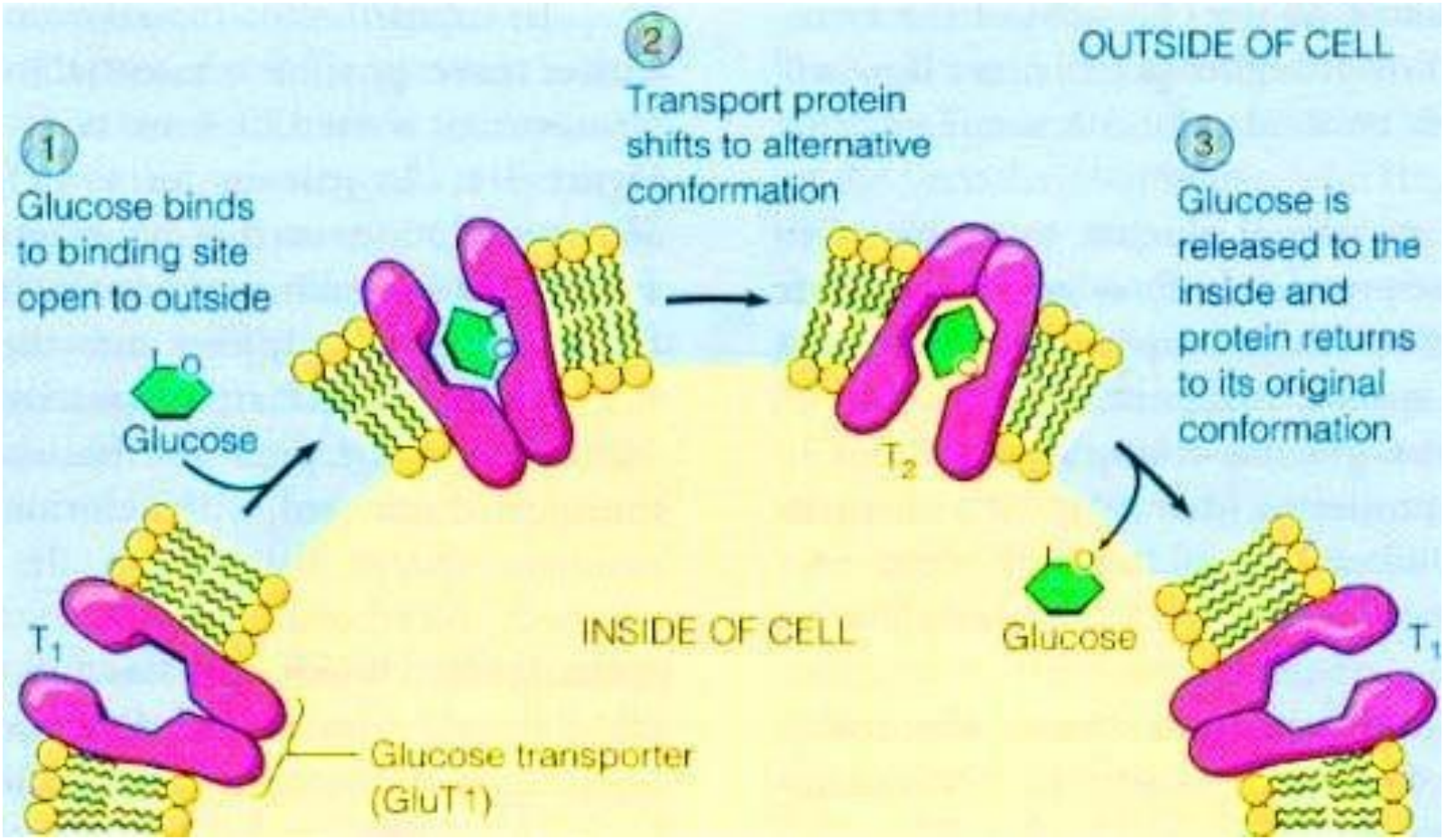
GLUCOSE TRANSPORT IN BLOOD

Glucose transporters (GLUT)

GLUT Isoform	K_m (substrate) mM	Tissue & Characteristics
GLUT-1	5 (glucose)	Resting glucose uptake in most cells, including muscle
GLUT-2	10-15 (glucose, [galactose & fructose])	Liver, pancreas β cells, kidney, enterocytes
GLUT-3	1-2 (glucose)	Mainly brain (note low K_m), also found at low levels in other tissues
GLUT-4	3-5 (glucose)	Insulin-sensitive tissues – Skeletal muscle, adipose tissue
GLUT-5	6 (fructose)	Jejunum

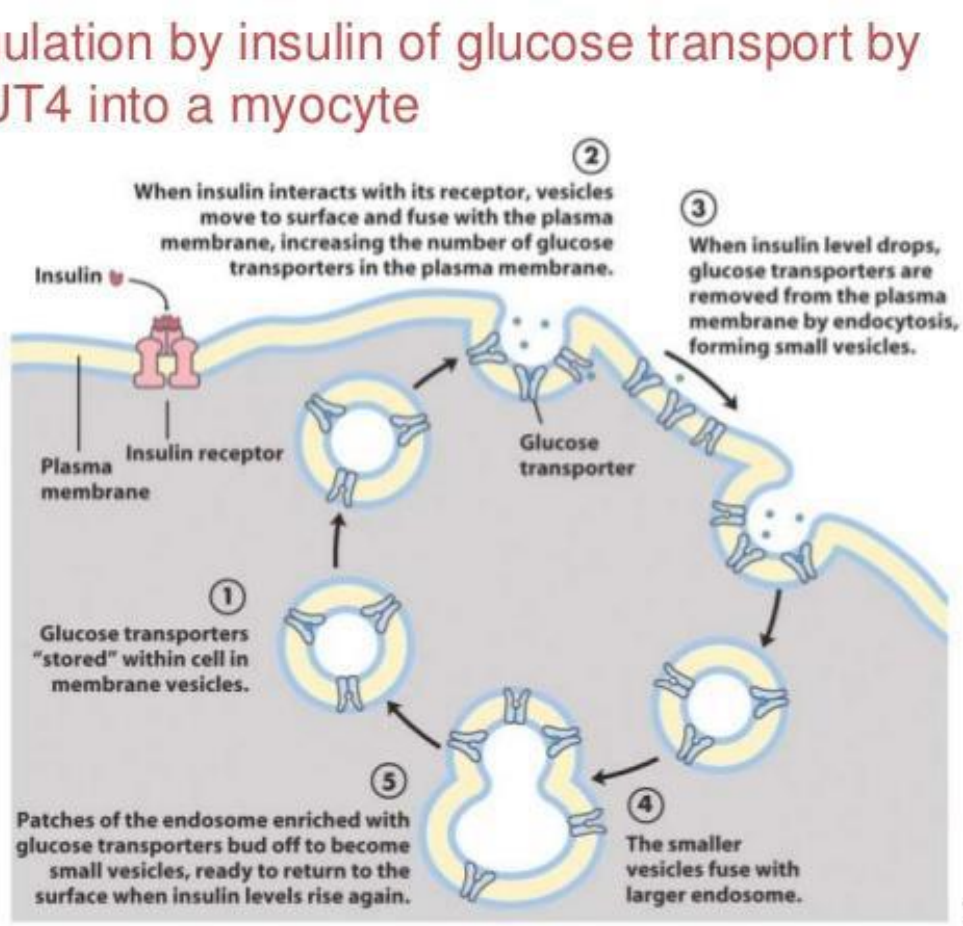
GLUCOSE TRANSPORT IN BLOOD

Glucose transporters (GLUT)



GLUCOSE TRANSPORT IN BLOOD

Glucose transporters (GLUT)



Type I (juvenile onset) diabetes mellitus

GLUCOSE TRANSPORT IN BLOOD

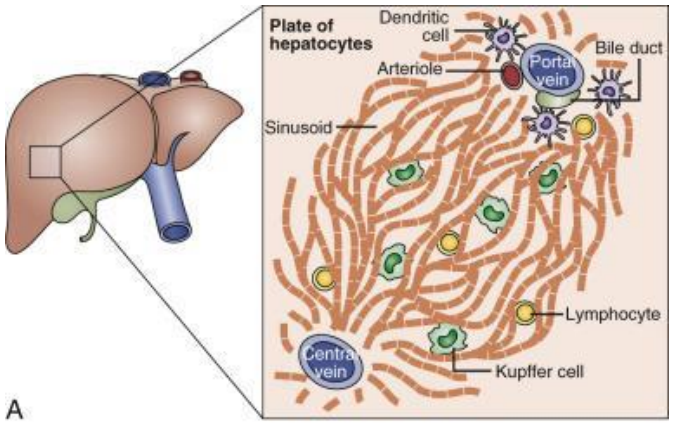
1) Intestine microvilli

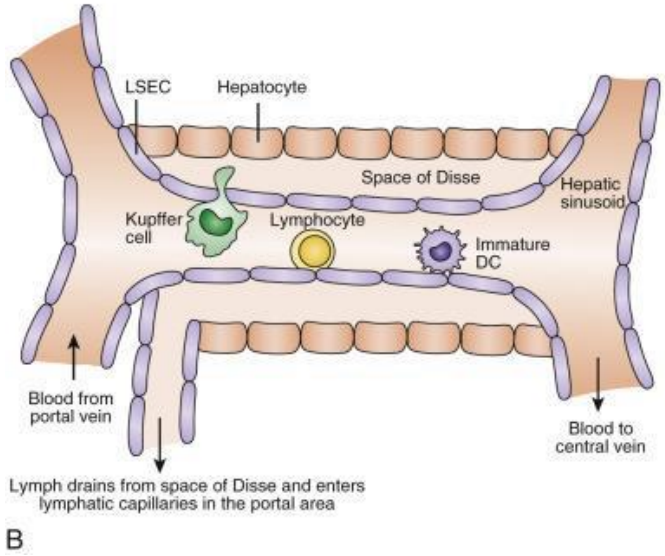
2) Blood of portal circulation

3) Sinusoides in liver lobule: here glucose enters hepatocytes after a meal.

4) Centrolobular vein

5) General circulation

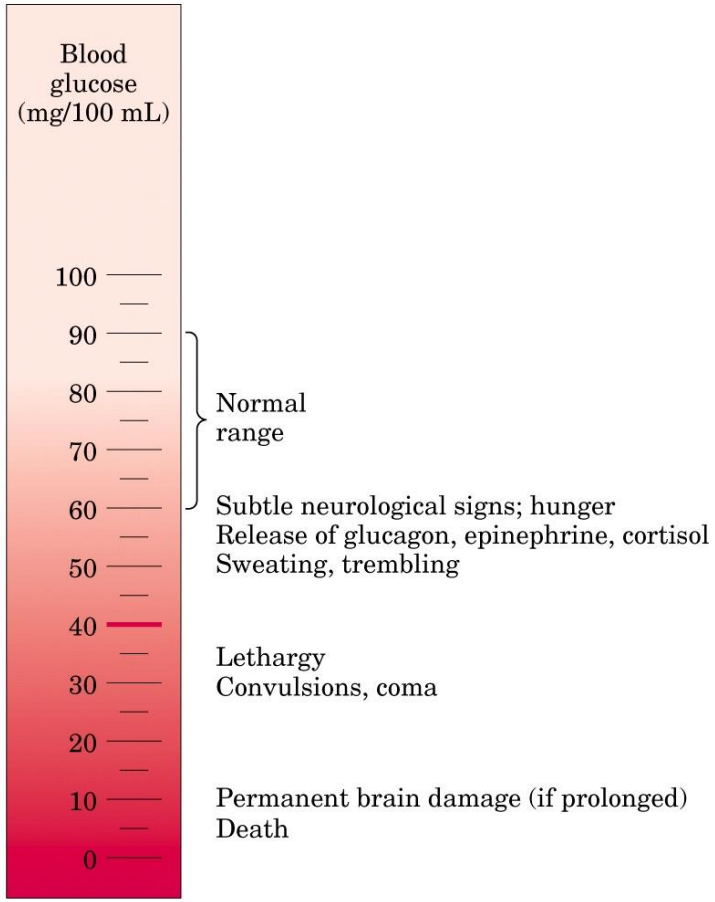




GLUCOSE TRANSPORT IN BLOOD

Glycaemic peak after a carbohydrate meal.

Glycaemic regulation: **insulin** and **glucagon**



GENERAL SCHEME OF CARBOHYDRATE METABOLISM

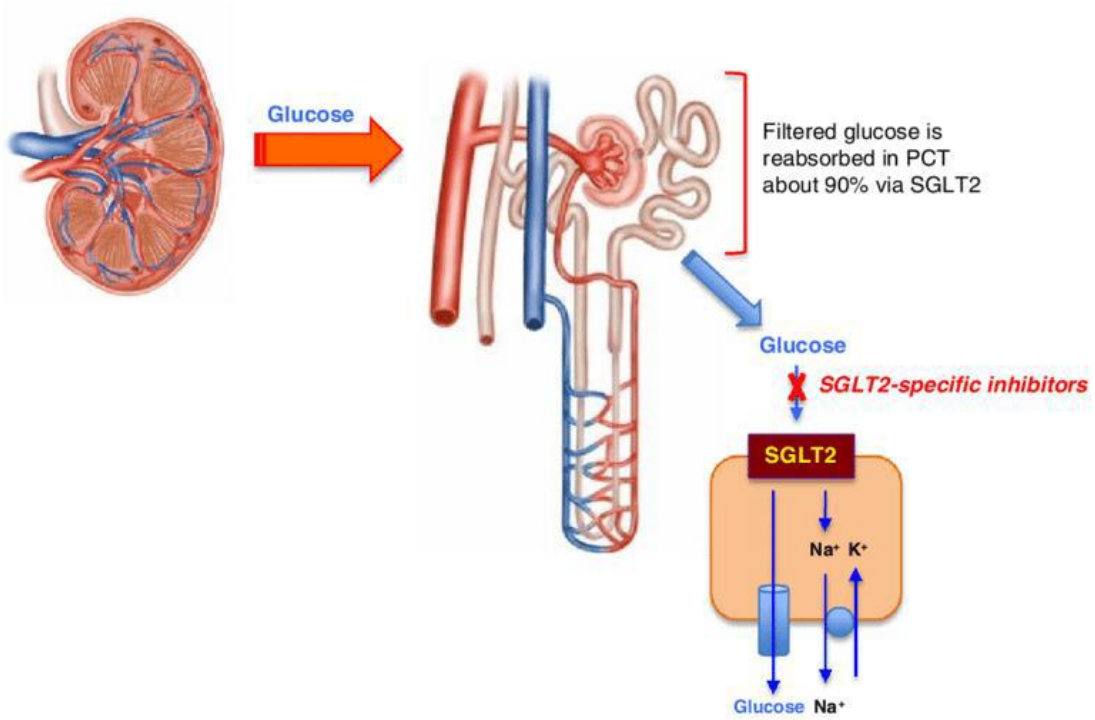
Distribution of metabolic tasks between **liver** and **peripheral tissues** (muscle, brain…) through blood circulation.

Role of **kidney**: ultrafiltration and reabsorption of glucose: *renal threshold.* Reabsorption of glucose refers to the process by which glucose is retrieved from the filtrate in the kidneys and returned to the bloodstream. This process is crucial for maintaining glucose homeostasis and preventing glucose loss in the urine.

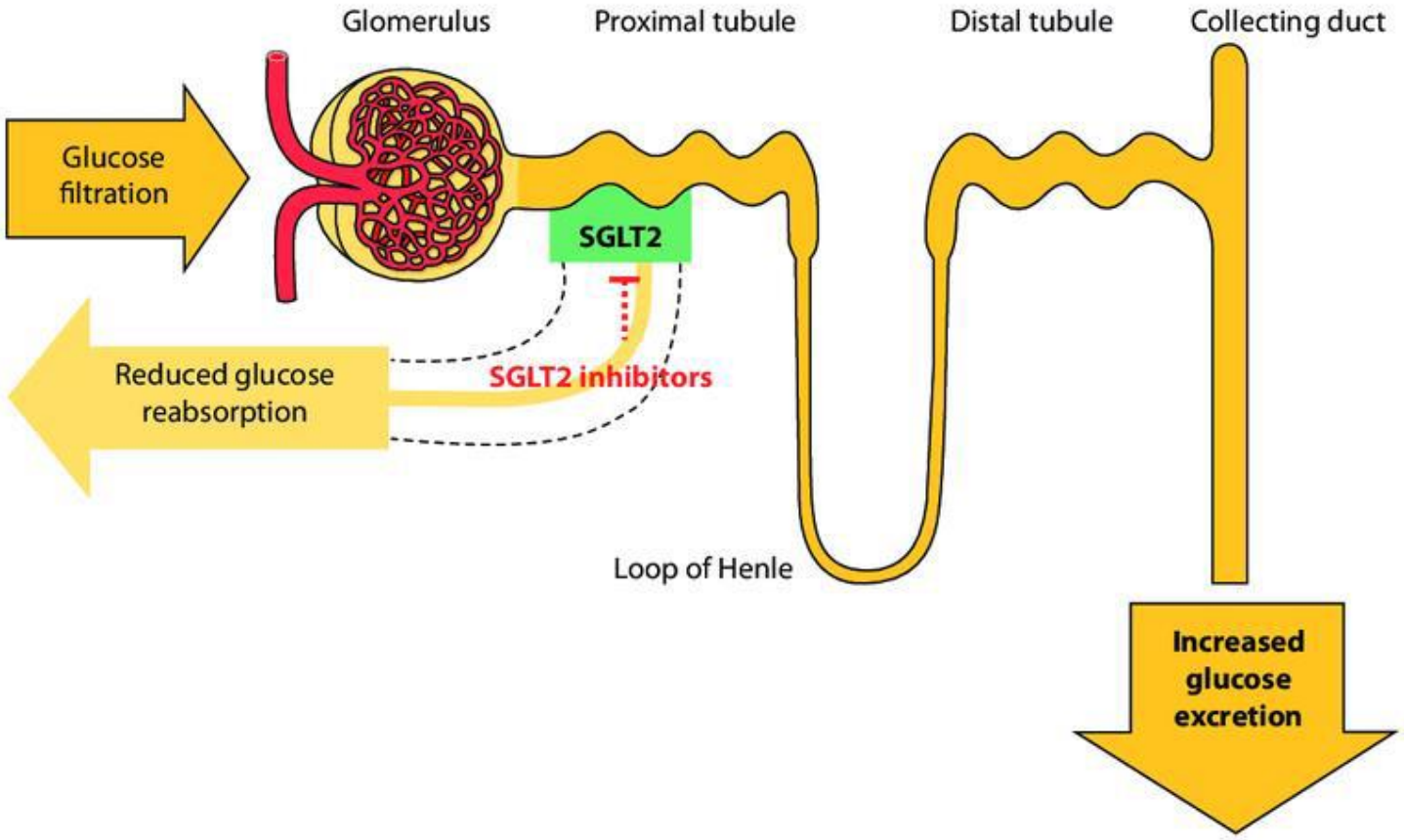
GLUCOSE REABSORPTION IN KIDNEY

The proximal convoluted tubule (PCT) is the primary site for glucose reabsorption in the kidneys.

Glucose is co-transported with sodium ions (Na^+) into PCT cells via sodium-glucose linked transporter 2 (SGLT2): SGLT2, a low-affinity, high-capacity transporter, reabsorbs 90% of filtered glucose in the early PCT.



GLUCOSE REABSORPTION IN KIDNEY



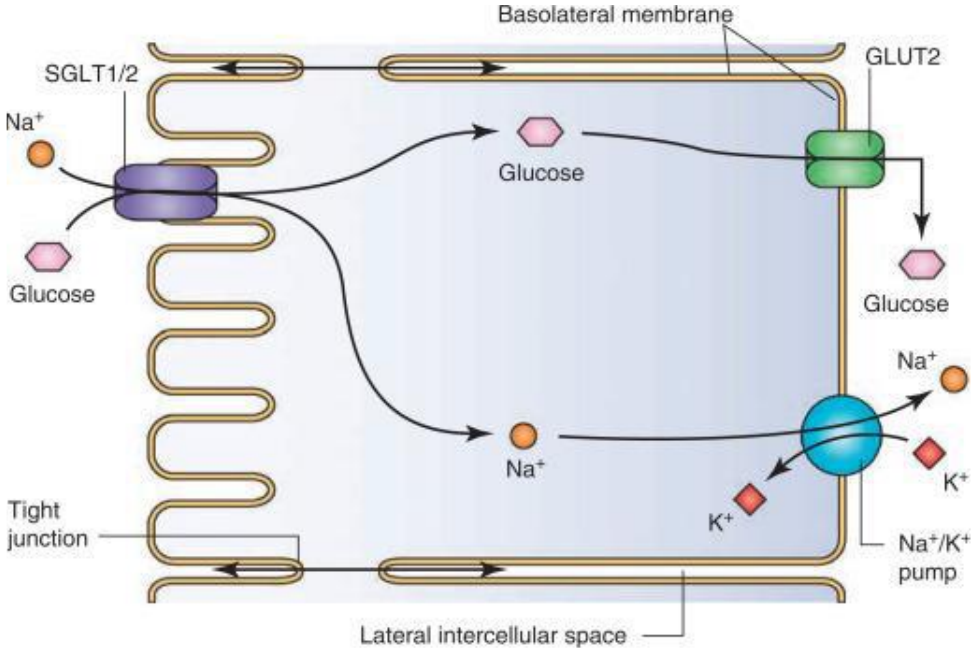
Reproduced with permission from Freeman JS. Review of insulin-dependent and insulin-independent agents for treating patients with type 2 diabetes mellitus and potential role for sodium-glucose co-transporter 2 inhibitors. Postgrad Med 2013;125(3):214–26.
SGLT2, sodium-glucose co-transporter 2

GLUCOSE REABSORPTION IN KIDNEY

The remaining 10% of glucose is reabsorbed in the later PCT by SGLT1, a high-affinity, low-capacity transporter.

Glucose exits into the bloodstream (Basolateral transport) via glucose transporters (GLUT2 and GLUT1).

The Na^+/K^+ ATPase pump provides the electrochemical gradient necessary for SGLT-mediated glucose uptake.



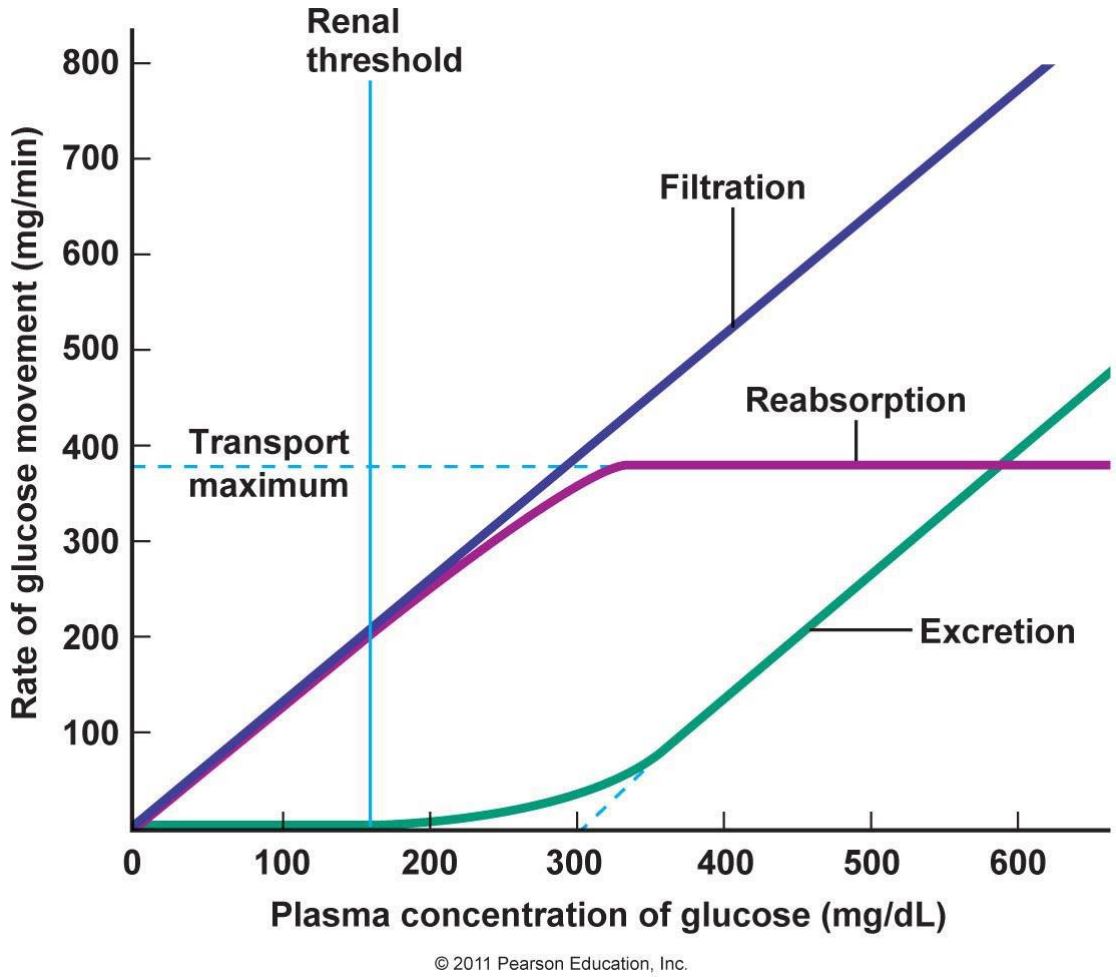
GLUCOSE RENAL THRESHOLD

The normal renal threshold for glucose (RTG) is the blood glucose concentration at which the kidneys begin to excrete glucose into the urine. In healthy individuals, this threshold is **approximately 180–200 mg/dL.** Below this range, nearly all filtered glucose is reabsorbed by sodium-glucose cotransporters (SGLTs) in the proximal convoluted tubule (PCT).

RTG can vary between individuals due to age, kidney function, and health status. For example:

- Pregnant individuals or children may have a lower RTG (< 126 mg/dL).
- In type 2 diabetes, RTG may rise to 200–250 mg/dL due to prolonged hyperglycemia and insulin resistance.

GLUCOSE RENAL THRESHOLD



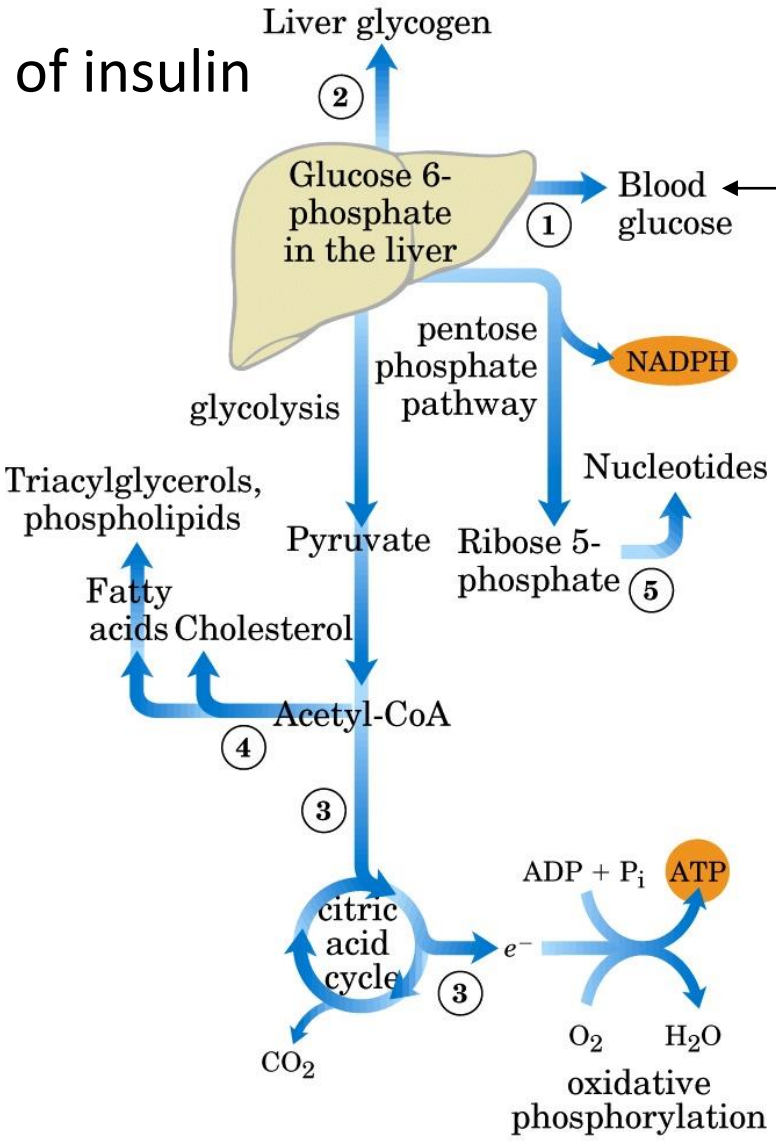
The transport maximum (T_m) for glucose reabsorption is 375 mg/min in men and 300 mg/min in women

EFFECTS OF INSULIN AND GLUCAGON

- **Insulin** activates all pathways that consume glucose:
  - glycogen synthesis
  - glycolysis
  - pentose pathway
  - lipid synthesis
- **Glucagon** activates all pathways that make glucose:
  - glycogenolysis
  - gluconeogenesis

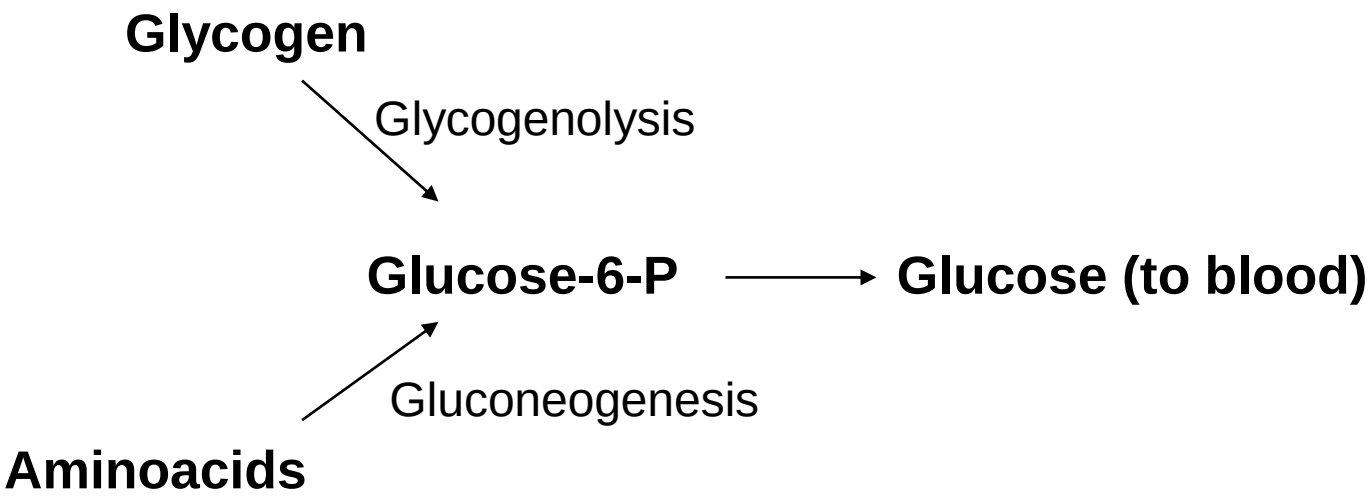
EFFECTS OF INSULIN AND GLUCAGON

After a meal: action of insulin



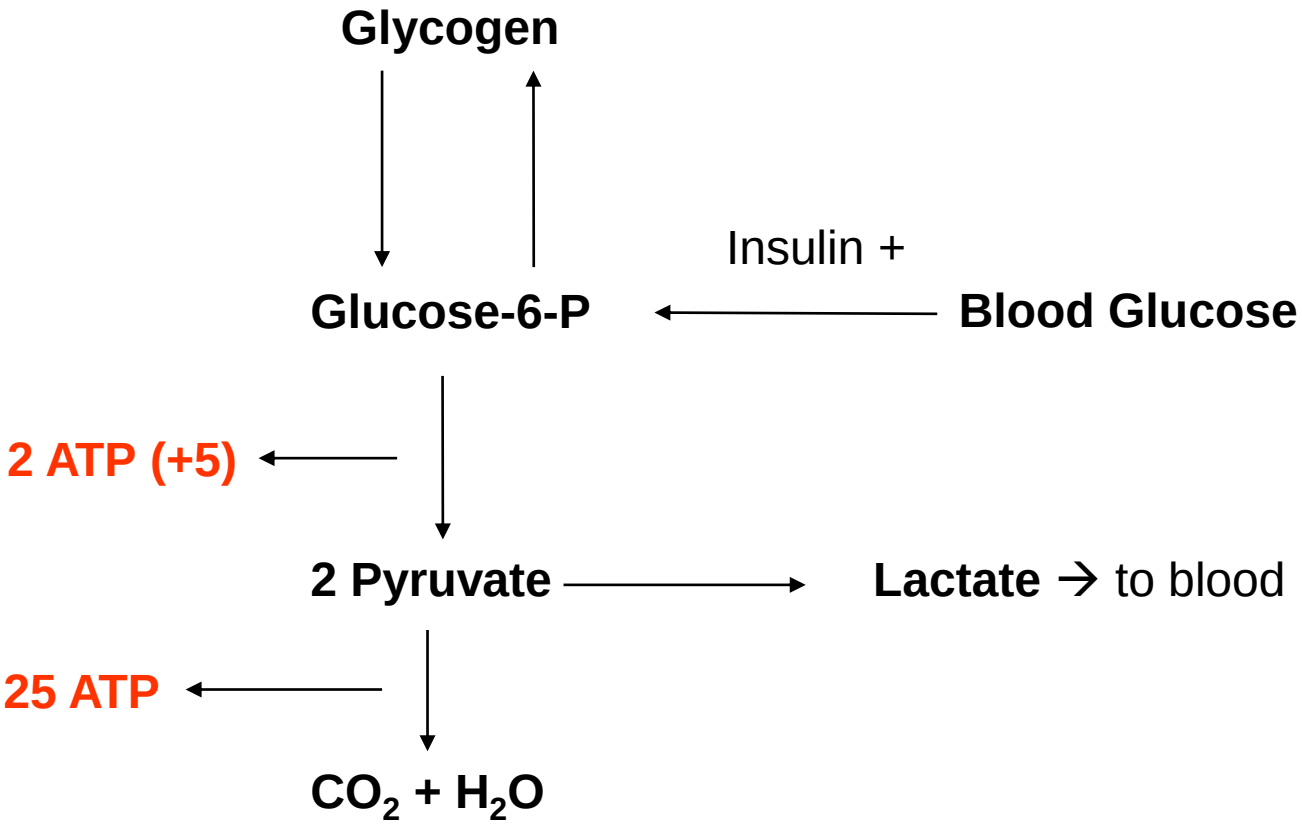
EFFECTS OF INSULIN AND GLUCAGON

Fasting conditions: glucagon actions in liver.



EFFECTS OF INSULIN AND GLUCAGON

In skeletal muscles:



KINASES AND PHOSPHATASES

Kinase is a common name for phosphotransferase

$$X + ATP \rightarrow X\text{-}P + ADP$$

In *protein kinases,* X is an aminoacid residue in a protein (Ser, Thr, Tyr).

Many kinases (but not all) catalyze irreversible reactions: in such cases the back reactions are usually catalyzed by phosphatases.

$$X + ATP \rightarrow X\text{-}P + ADP$$

$$X\text{-}P + H_2O \rightarrow X + P_i$$

GLUCOSE PHOSPHORYLATION

Hexokinase and glucokinase:

glucose + ATP → glucose-6-P + ADP

Glucose-6-phosphatase (only in liver and kidney):

glucose-6-P + H_2O → glucose + P_i

Futile Cycle:

glucose + ATP + H_2O → glucose + ADP + P_i

Such a futile cycle is largely prevented by hormonal regulation.

GLUCOSE PHOSPHORYLATION

Transcriptional control

Glucokinase

Insulin + Glucagon – → *Decrease of glycemia*

Glucose-6-Pase

Glucagon+ Insulin – → *Increase of glycemia*

GLUCOSE PHOSPHORYLATION

The liver produces glucose for other tissues

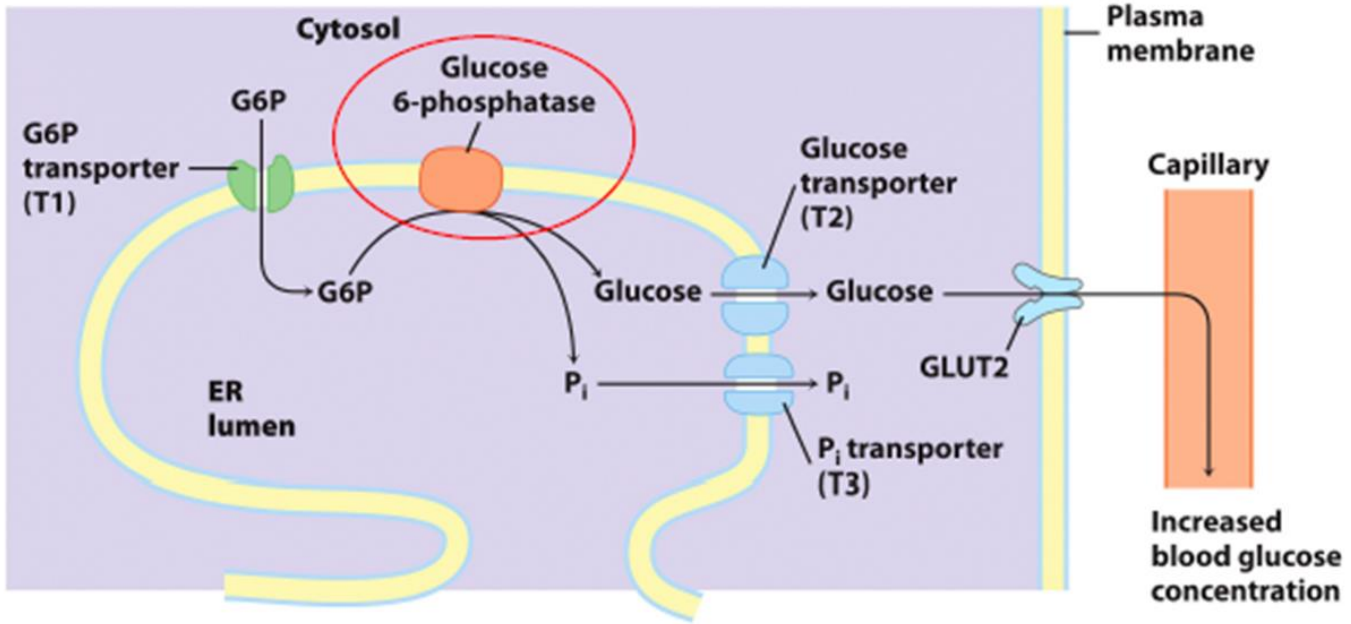
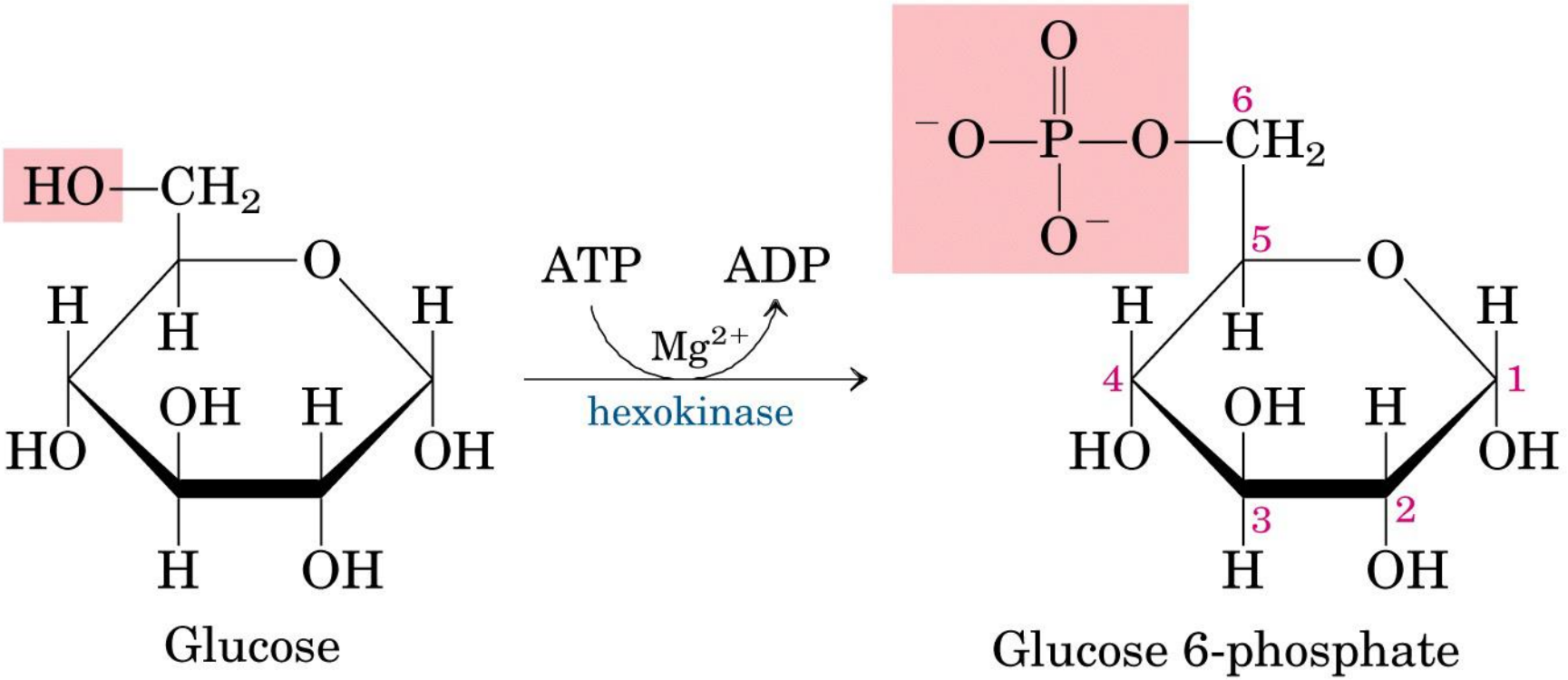


Figure 15-30
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

Glucose 6-phosphatase

- Expressed only in liver & kidney
- Integral membrane protein in the ER – has 9 transmembrane helices
- Genetic defects cause Type Ia (von Gierke) glycogen storage disease

GLUCOSE PHOSPHORYLATION



Glucose

Glucose 6-phosphate

$$\Delta G'^{\circ} = -16.7 \text{ kJ/mol}$$

GLUCOSE PHOSPHORYLATION

Glucokinase (GK)

Liver and pancreatic cells

Low affinity, specific to glucose

Not inhibited by G6P

Induced by insulin

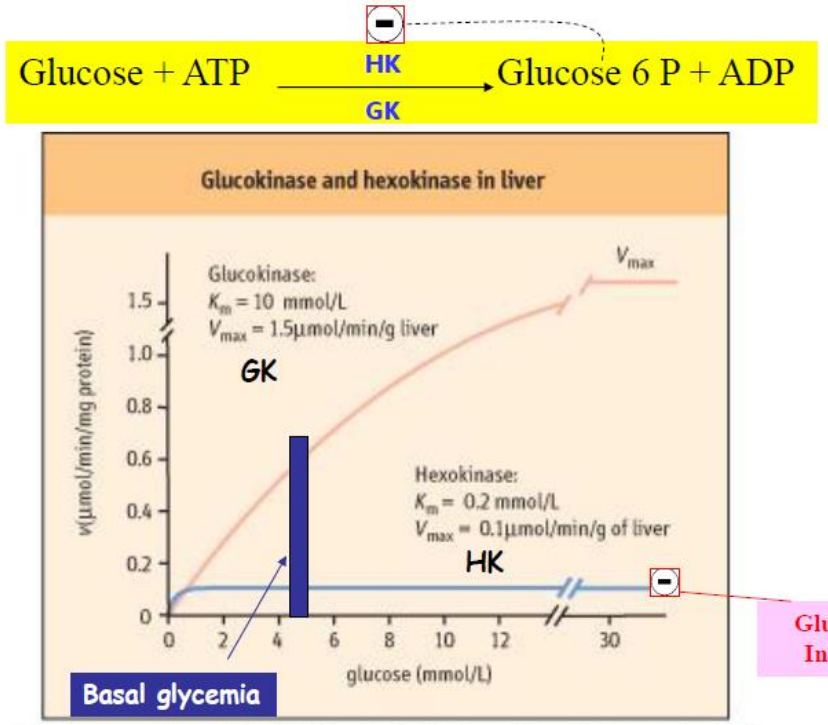
Hexokinase (HK)

All other tissues

High affinity to glucose, fructose and mannose

Inhibited by G6P

Not induced by insulin



GLUCOSE PHOSPHORYLATION

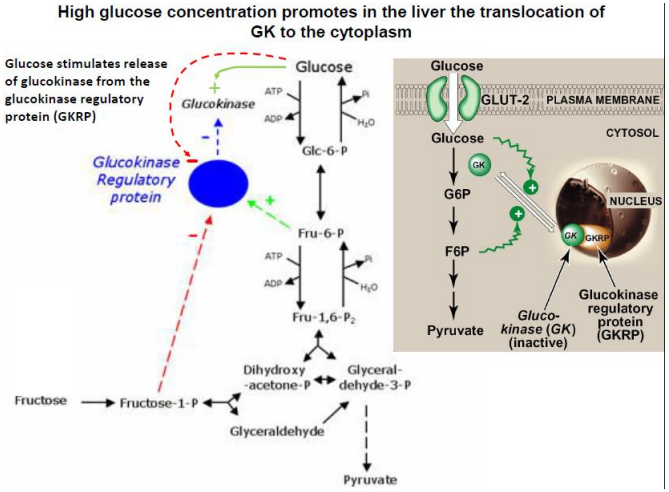
The glucokinase regulatory protein (GKRP), regulates the activity of glucokinase (GCK) in liver.

GKRP sequesters GCK in the nucleus during fasting, creating a reserve that is rapidly mobilized postprandially.

High glucose levels promote GCK release into the cytoplasm for glucose phosphorylation and glycogen synthesis.

F6P stabilizes the GCK-GKRP complex, enhancing inhibition.

F1P disrupts the complex, releasing active GCK into the cytosol.



GLUCOSE PHOSPHORYLATION

Glycogen synthesis

Glycolysis

Pentose-P pathway

All stimulated by insulin and inhibited by glucagon

Credits:

Prof. Michele Di Foggia

Dipartimento di Scienze Biomediche e Neuromotorie – Sezione di Biochimica
via Irnerio 48
Telephone: +39 051 2094281

michele.difoggia2@unibo.it

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA