Glucose metabolism

cata → Glycolysis

Ana → Gluconeogenises

my girl ♥

Sarah

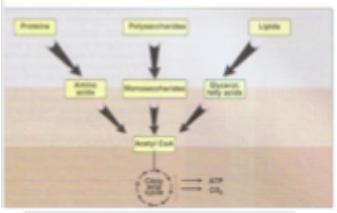
♥ ♥ ♥ ♥ ♥ ♥ ♥ ♥ ♥

mommy "♡"

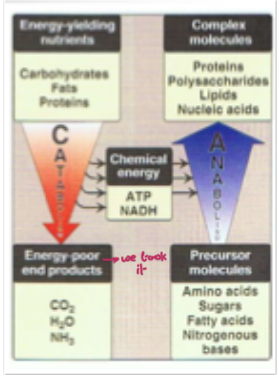
Metabolism

- Most pathways can be classified into:

use ATP to produce → more ATP



Catabolism: degrade complex molecules (proteins, carbohydrate and triglycerides) to few simple products (CO_2, NH_3 and H_2O). Capture chemical energy to form ATP. Considered a **convergent** process (large no. of substances are degraded to few common end products).



Anabolism: synthesize complex end products from simple precursors. Requires energy which is provided by the breakdown of ATP. Considered a **divergent** process (few starting precursors produce wide variety of complex substances)

Regulation of metabolism

- ① Signals from within the cell (intracellular)

  The rate of a metabolic pathway may be influenced by the availability of substrates, product inhibition, or alterations in the levels of allosteric activators or inhibitors.

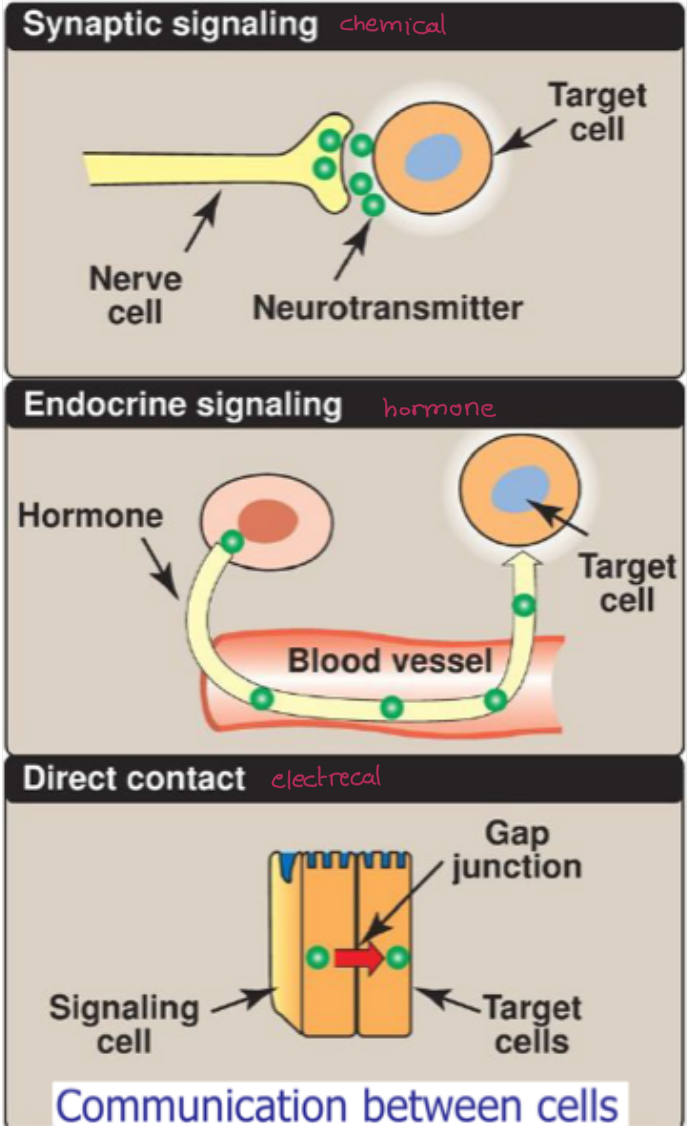
- ② Communication between cells (intercellular)

  Can be mediated by surface-to-surface contact, hormones and, in some tissues, by formation of gap junctions

- ③ Second messenger systems

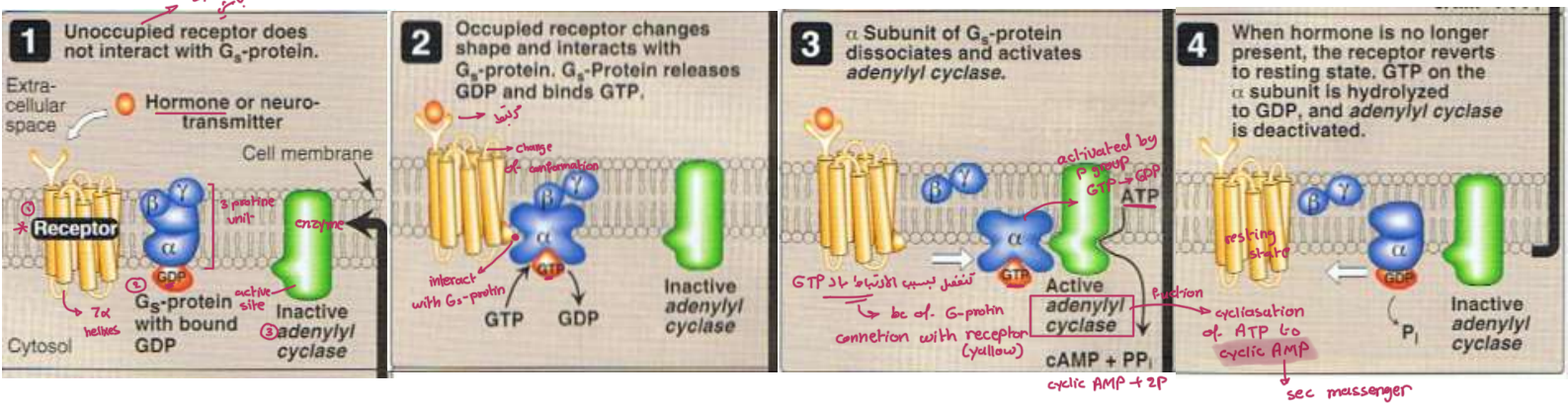
  Two of the most widely recognized second messenger systems are:

  - The calcium/phosphatidylinositol system
  - The adenylyl cyclase system

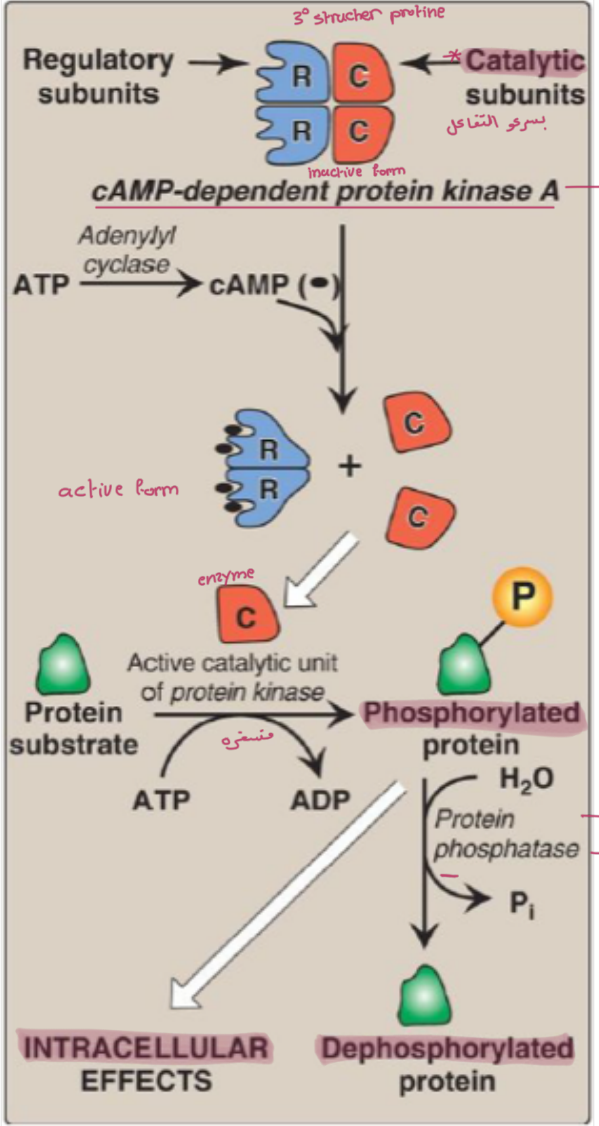

Synaptic signaling
chemical
Target cell
Nerve cell
Neurotransmitter
Endocrine signaling
hormone
Hormone
Target cell
Blood vessel
Direct contact
electrecal
Gap junction
Signaling cell
Target cells
Communication between cells

Regulation of metabolism
Adenylyl cyclase

① Glocagon (hormon)
② ep/nor·ep (Nurotransmiters)
③ corticohorsteros (hormon)



1. GTP-dependent regulatory proteins (Gs and Gi-proteins)
2. Protein kinases: phosphorylates different proteins and enzymes
3. Dephosphorylation of proteins: Phosphatases reverse the effect of kinases.


3° structure protine
Regulatory subunits
R
C
R
C
Catalytic subunits
بسرع التفاعل
Inactive form
cAMP-dependent protein kinase A
enzyme → phosphorelte other enzyme
Adenylyl cyclase
ATP
cAMP (•)
active form
R
R
+
C
C
enzyme
C
P
Active catalytic unit of protein kinase
Protein substrate
Phosphorylated protein
مستعرة
ATP
ADP
H_2O
Protein phosphatase
enzyme → dyphosphlation
P_i
INTRACELLULAR EFFECTS
Dephosphorylated protein

Transport of glucose to cells

① Na-independent → facilitated diffusion

② Na-dependent → Na-monosaccharide cotransporter system

- Glucose cannot diffuse directly into cells, but enters by one of two transport mechanisms:
- Na-independent, facilitated diffusion transport system

① Na-independent (facilitated diffusion):

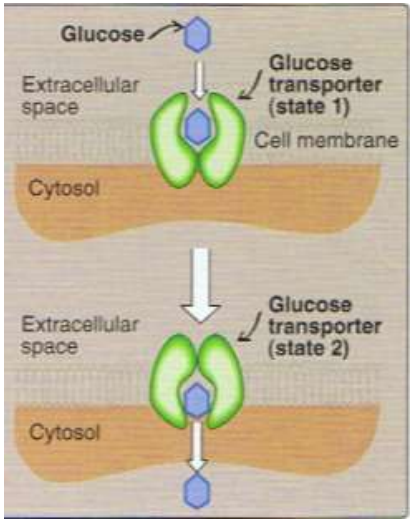
- In facilitated diffusion, glucose movement follows a concentration gradient → no energy needed
- Tissue specificity of GLUT gene expression:

كل خلية لها نوع معين من ال GLUT لنقل الغلوكوز ← transporters of glucose

1. GLUT-3 is the primary glucose transporter in neurons
2. GLUT-1 is abundant in erythrocytes and brain, but is low in adult muscle
3. GLUT-4 (in adipose tissue and skeletal muscle). Their number is increased by insulin → بدون انسولين GLUT-4 كثير قليل ← وزاكم في الدم
4. GLUT-2 (in the liver, kidney, and β cells of the pancreas) can either transport glucose into these cells or from it depending on blood glucose levels → also intestine cells

معصين (1-6)

معين ↓ works two directions



Transport of glucose to cells

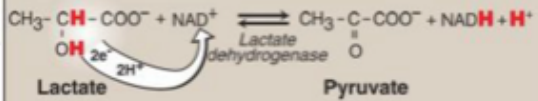
5. GLUT-5 is the primary transporter for fructose in the small intestine and the testes

6. GLUT-7 (in the liver and other gluconeogenic tissues) mediates glucose flux across the endoplasmic reticular membrane.

Na-monosaccharide cotransporter system: is an energy-requiring process that transports glucose against a conc. gradient

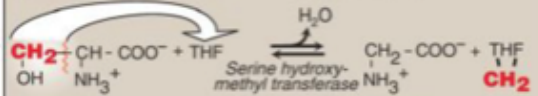
- This system is a carrier-mediated process in which the movement of glucose is coupled to the conc. gradient of Na, which is trasported into the cell at the same time.
- It occurs in the epithelial cells of the intestine, renal tubules, and Choroid plexus.
- This system is mediated by a family of fourteen glucose transporters in cell membranes (GLUT-1 to GLUT-14)
- They exist in the membrane in two conformational states. Extracellular glucose binds to the transporter, which then alters its conformation, transporting glucose across the cell membrane.

1. *Oxidoreductases* Catalyze oxidation-reduction reactions, such as:



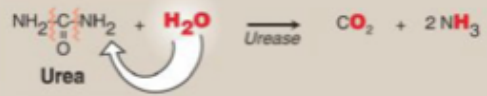
Lactate → Pyruvate

2. *Transferases* Catalyze transfer of C-, N-, or P-containing groups, such as:



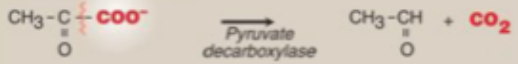
Serine → Glycine

3. *Hydrolases* Catalyze cleavage of bonds by addition of water, such as:



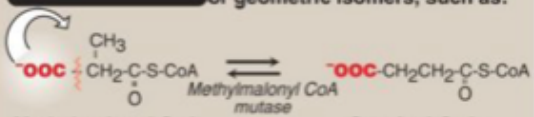
Urea

4. *Lyases* Catalyze cleavage of C–C, C–S, and certain C–N bonds, such as:



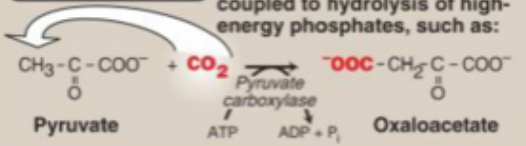
Pyruvate → Acetaldehyde

5. *Isomerases* Catalyze rearrangement of optical or geometric isomers, such as:



Methylmalonyl CoA → Succinyl CoA

6. *Ligases* Catalyze formation of bonds between carbon and O, S, and N coupled to hydrolysis of high-energy phosphates, such as:



Pyruvate → Oxaloacetate

Energy metabolism cycles

Energy metabolism is the process of generating energy (ATP) from nutrients, starts by glycolysis and ends with oxidative phosphorylation

1) Catabolism: cellular respiration

2) Anabolism: Gluconeogenesis

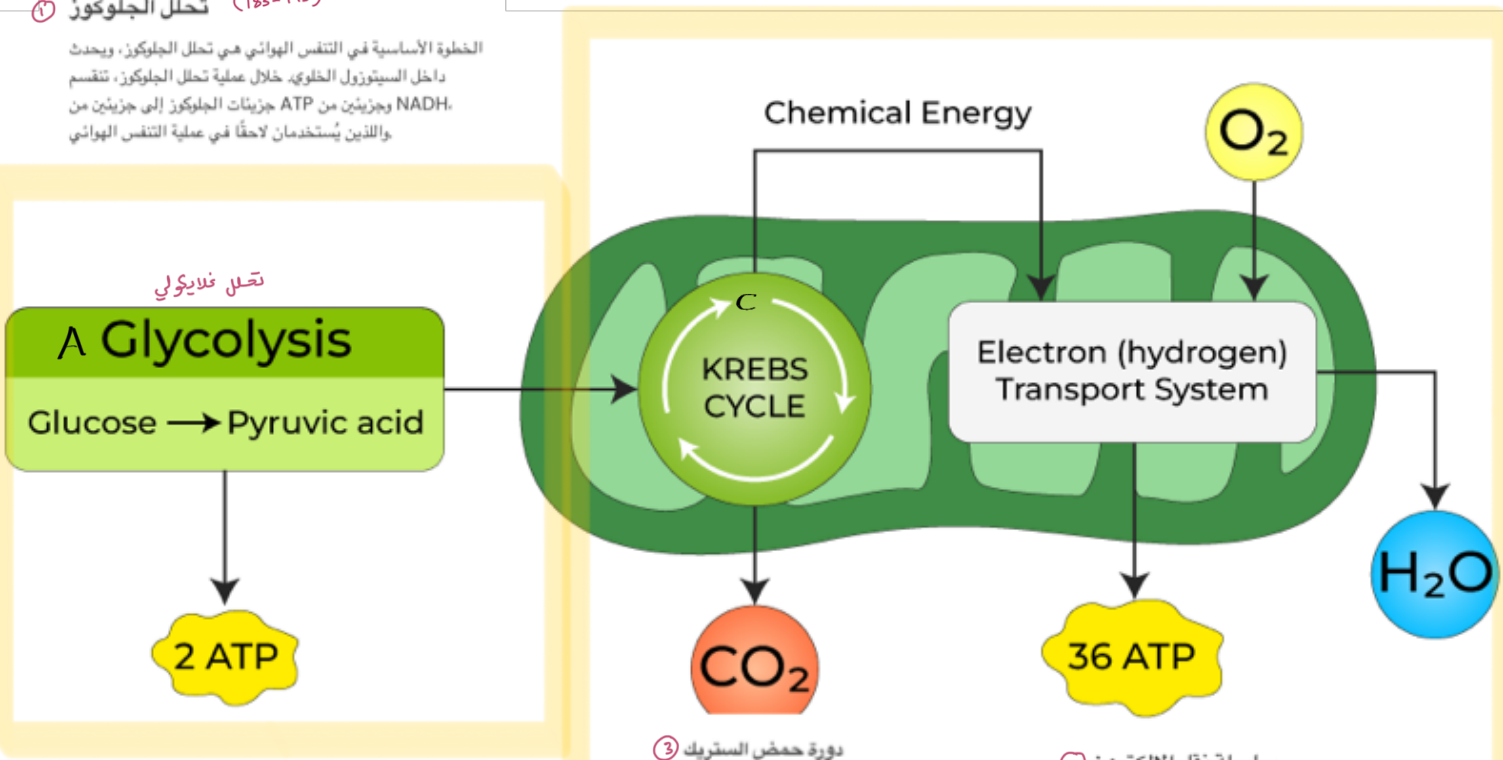
1) Cellular respiration

خطوات التنفس الهوائي

يتم عملية التنفس الهوائي بالكامل في أربع مراحل مختلفة

① تحلل الجلوكوز (188-195)

الخطوة الأساسية في التنفس الهوائي هي تحلل الجلوكوز، ويحدث داخل السيتوزول الخلوي. خلال عملية تحلل الجلوكوز، تنقسم جزيئات الجلوكوز إلى جزيئين من ATP وجزيئين من NADH، واللذين يُستخدمان لاحقًا في عملية التنفس الهوائي.



② تكوين أسيتيل مرافق الإنزيم أ B

الخطوة الثانية في التنفس الهوائي هي تكوين أسيتيل مرافق الإنزيم أ. في هذه العملية، يتأكسد البيروفات في الميتوكوندريا، وتنتج مجموعة أسيتيل ثنائية الكربون. ترتبط مجموعة الأسيتيل ثنائية الكربون الناتجة حديثًا مع مرافق الإنزيم أ، منتجةً أسيتيل مرافق الإنزيم أ. (197 /198)

③ دورة حمض الستريك

الخطوة الثالثة في التنفس الهوائي هي دورة حمض الستريك، والتي تُسمى أيضًا دورة كريبس. في هذه المرحلة من التنفس الهوائي، يتحد أوكسالوأسيتات مع أسيتيل مرافق الإنزيم أ، مُنتجًا حمض الستريك. تخضع دورة حمض الستريك لسلسلة من التفاعلات، وتُنتج أيضًا ATP، جزيئين من ثاني أكسيد الكربون، وجزيء واحد من NADH وFADH، مُختزلة من (199 – 202)

④ سلسلة نقل الإلكترون

هذه هي الخطوة الأخيرة في التنفس الهوائي. في هذه المرحلة، تُنتج NADH بنقل الإلكترونات من ATP كميات كبيرة من جزيئات FADH. يُنتج جزيء واحد من الجلوكوز ما مجموعه 34 جزيئًا من ATP.

A

* Oxidation of glucose

Glycolysis

O2 ↓ Aerobic : pyruvic acid

O2 ↓ Anaerobic : Lactic acid

- Glycolysis occurs in the cytosol of all tissues and cells
- Defined as oxidation of glucose to pyruvic acid (in the presence of O_2, Aerobic) and to lactic acid (in the absence of O_2, anaerobic)
- The catabolism of 1 mol of glucose (6 C) produces 2 moles of pyruvate or lactate (3 C)
- Lactate is produced only in:
  1. RBC: as there is no mitochondria
  2. Exercising muscles: lack of O_2

1 mol Glucose (6C)

↓

A → 2 moles pyruvate (3C)

or

Ana → 2 moles lactate (3C)

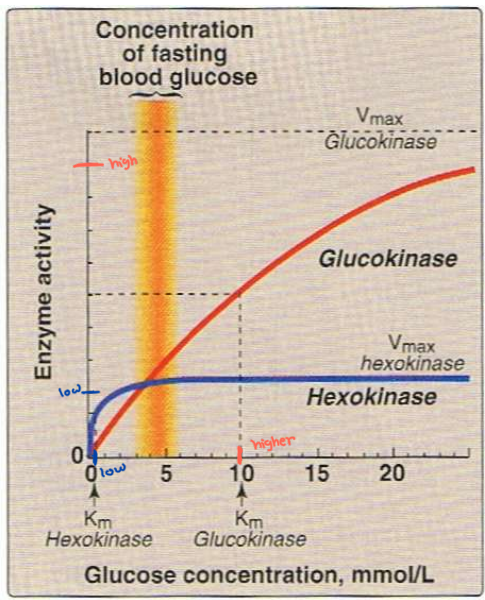
Phosphorylation of glucose

First step to glycolysis , After glucose had entered the cell (not in blood)

- Phosphorylated sugar molecules do not readily penetrate cell membranes (no carriers, too polar to cross) → عشان كذا بعمل فسفره بعد ما يدخل → adding phosphate on C→6 (ما لو نواقل)
- Hexokinase has broad substrate specificity (not just glucose) and it is inhibited by the reaction product, glucose 6-phosphate

Glucose ①Hexokinase / ②Glucokinase → Glucose 6-pho

- It has a low Km (high affinity) for glucose and low Vmax
- Glucokinase (similar broad specificity): In liver parenchymal cells and islet cells of the pancreas
- In β cells, glucokinase functions as the glucose sensor, determining the threshold for insulin secretion. In the liver, the enzyme facilitates glucose phosphorylation during hyperglycemia.
- Glucokinase functions only when the intracellular concentration of glucose in the hepatocyte is elevated, such as during the brief period following consumption of a carbohydrate- rich meal



found within the whole body

Enzymes of glucose phospho-

compare \ enzyme	Hexokinase	Glucokinase
sub. specifity	both has boroad sub. specifity (phosphorylate a wild range of suger)	
km (affinity)	low km → high affinity: بشتغل لما كمية السكر الداخله للخليه قليله ← يكسر كميات قليله ← كمية قليله من السكر كافيه تعمل sal إلو .	high km → low affinity بشتغل مع كميات سكر كبيره . * only functions when intracellular conc of glucose in hepatocytes is elevated
V_{max}	Low	high
Notes	Inhibited by the reaction product: (glucose 6-phosphate)	- very imp in: ① liver (parenchymal cells) facilitates glucose phos. during hyperglycemia ② islet cells of pancreas ↳ in β cells → glucokainase works as a sensor of insulin

Steps of glycolysis

I Energy investing phase: (استثمار الطاقه)

فسفره **Step 1:** glucose is phosphorylated to glucose-6-phosphate. The reaction is irreversible and is catalyzed by either glucokinase (GK) in liver cells and hexokinase (HK) in other tissues.

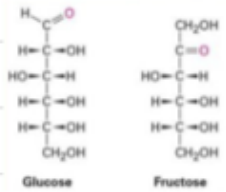
isomerisation **Step 2:** glucose-6-phosphate is isomerized to fructose-6-phosphate by isomerase enzyme

فسفره **Step 3:** fructose-6-phosphate is phosphorylated to F-1,6-diphosphate. The reaction is catalyzed by phosphofructo-kinase (PFK).

Step 4: F-1,6-bP is split by aldolase into two trioses (Glyceraldehyde-3-P and dihydroxyacetone phosphate)

Step 5: DHAP is isomerized to G-3-P which is catalyzed by isomerase

* Remeber:



II- Energy generating phase: (انتاج الطاقه)

Step 6:
G-3-P is oxidized phosphorylated forming 1,3-biphosphoglycerate (1,3-BPG) and NADH which is catalyzed by glyceraldehyde 3-P dehydrogenase. NADH produces 2.5 ATP in ETC.

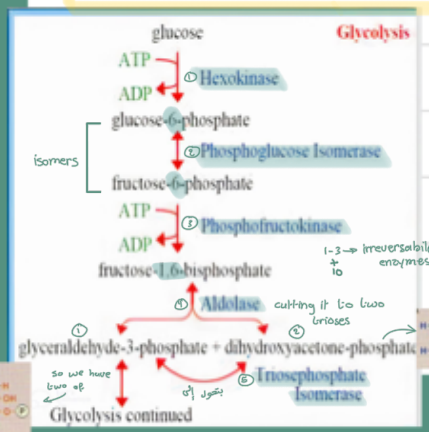
Step7: 1,3-BPG gives its high energy phosphate to ADP to form ATP converting to 3-PG. This is catalyzed by phosphoglycerate kinase.

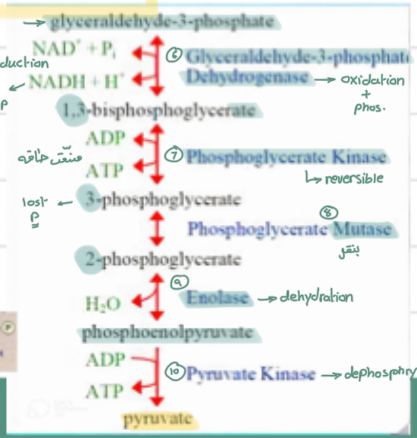
Step 8: 3-PG is converted to 2-phosphoglycerate by mutase

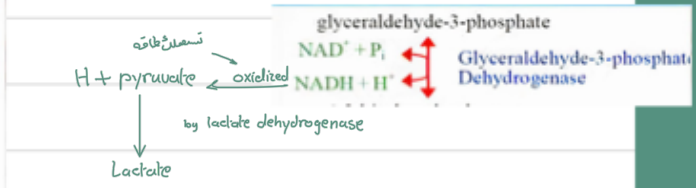
Step 9: Enolase enzyme dehydrates 2-PG forming 2-phosphoenol pyruvate (PEP)

Step 10: PEP is dephosphorylated giving its P to ADP to form ATP and converted to pyruvate. Rxn is irreversible and catalyzed by pyruvate kinase.

Step 11: in RBC's and under anaerobic conditions NADH formed in step 6 is oxidized to give hydrogen and pyruvate which converts into lactate by lactate dehydrogenase







Glucose ① hexkinas ② Glucokinas → Glucose-6-phosphat → (phospho glucose isomeris) → Fructose-6-phosphat → (phosphofructokinas) → 1,6-biphosphofructose

1,6-biphosphofructose → (Aldolase) → dihydroxyacetone ⇄ 3-glycelaldyhde (Triosephospate isomeres)

النواتج :

2 Glyceraldyhde-3-P

NAD+ → realu → NAH

oxi + phophorilation dyhyroclenase

1,3-bi-P-Glycerate

ADP → ATP

phosphoglycerate kinase (dePhosphoration)

3-P-Glycerate

Mutase

2-P-Glycerate

dehydrate by Enolase → H_2O

2-P-pyruvate

ADP → ATP

dephosphoration by : pyruvate kinase

Pyruvate

Anaerobic

pyruvate + H → (oxi) NAH

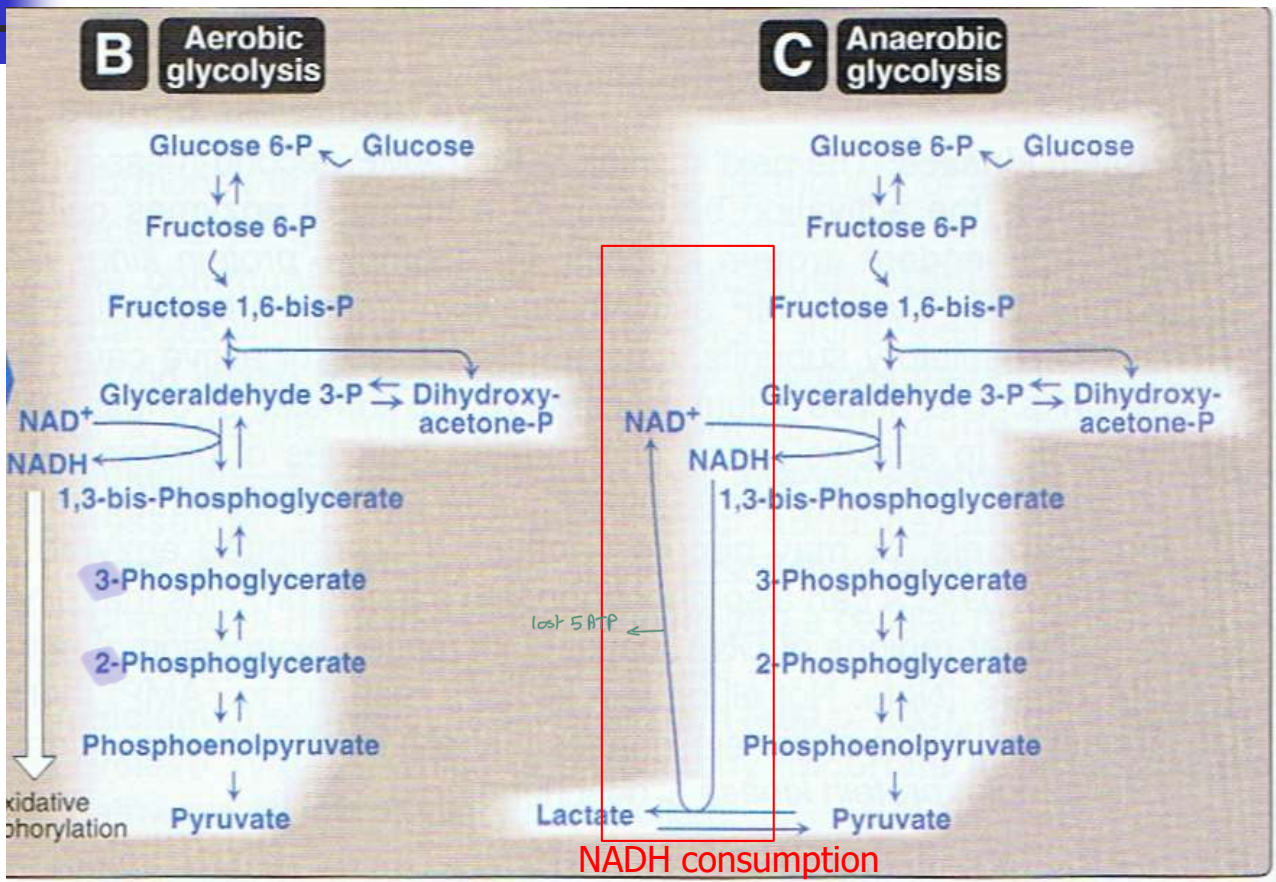
lactate dehydrogenase

Lactate

Lo

Step 11: in RBC's and under anaerobic conditions NADH formed in step 6 is oxidized to give hydrogen and pyruvate which converts into lactate by lactate dehydrogenase

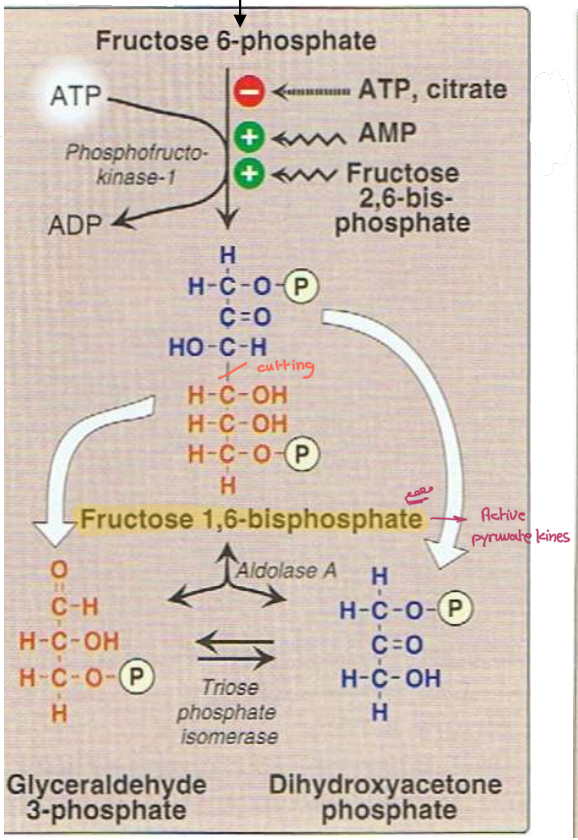
Schematic representation

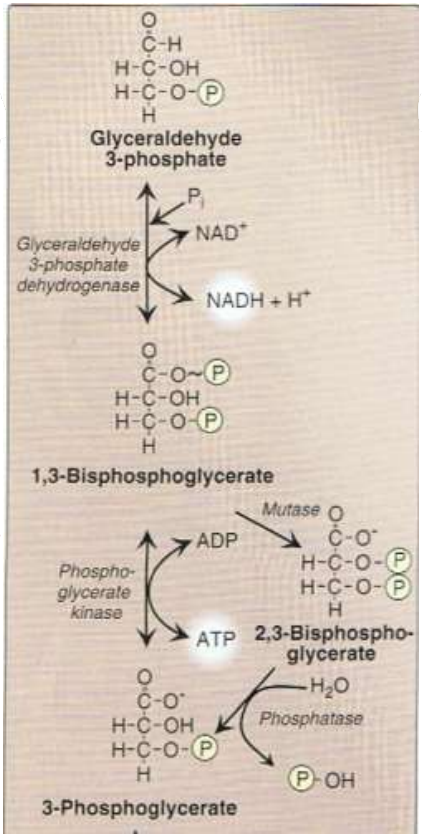


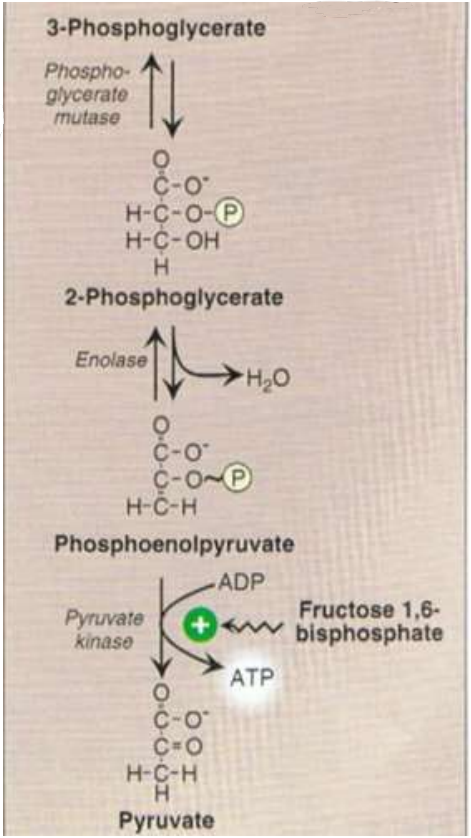
summary : Glucose

ATP → ADP

G-6P



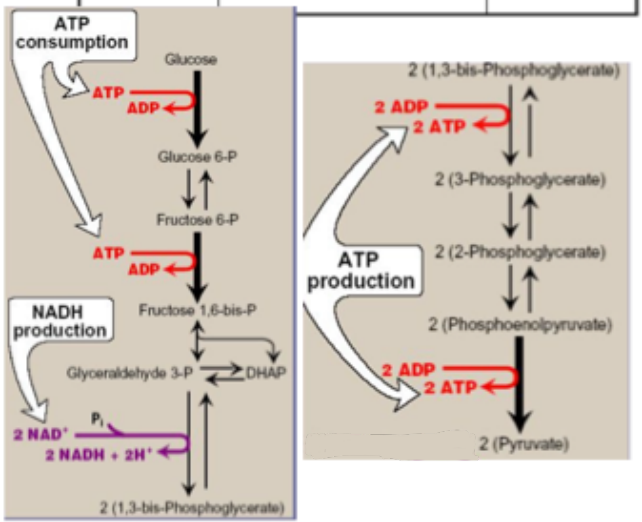




Energy gain

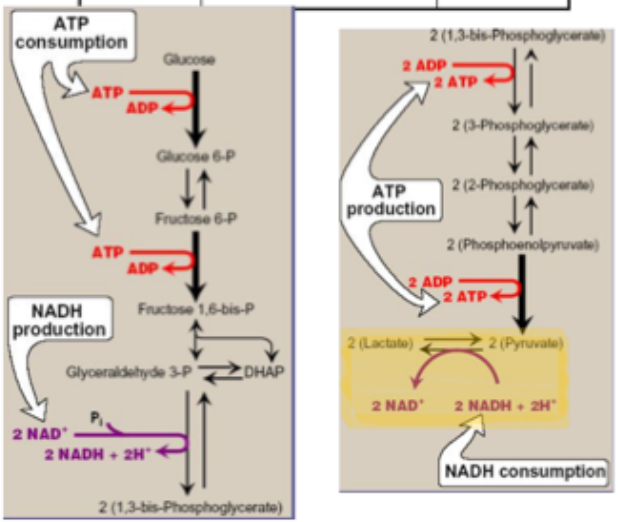
aerobic glcolysis

Step 1	Glucokinase (GK)	- 1 ATP
Step 3	Phosphofructokinase (PFK)	- 1 ATP
Step 7	Phosphoglycerate kinase	+ 2 ATP
Step 10	Pyruvate kinase (PK)	+ 2 ATP
Step 6	2 NADH	+ 5 ATP
Net gain		+ 7 ATP



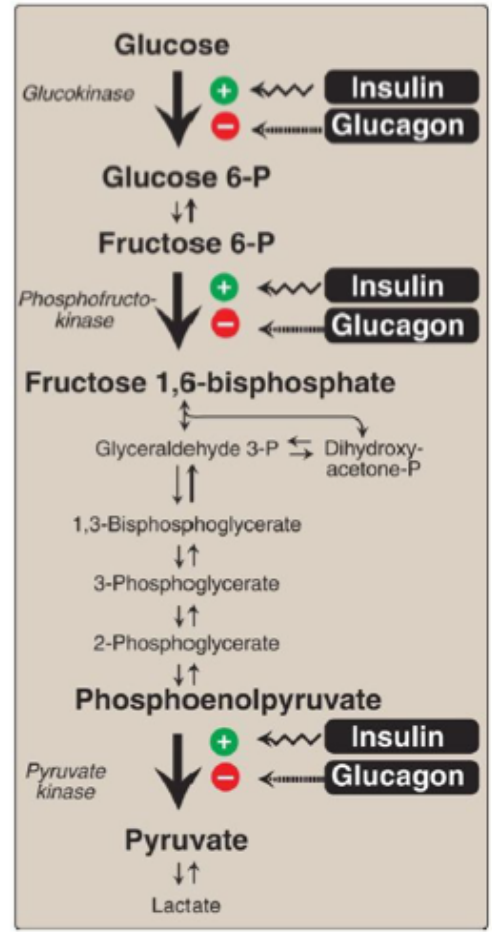
Anaerobic glycolysis

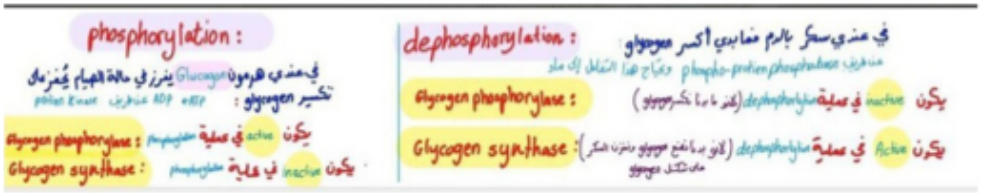
Step 1	Glucokinase (GK)	- 1 ATP
Step 3	Phosphofructokinase (PFK)	- 1 ATP
Step 7	Phosphoglycerate kinase	+ 2 ATP
Step 10	Pyruvate kinase (PK)	+ 2 ATP
Net gain		+ 2 ATP

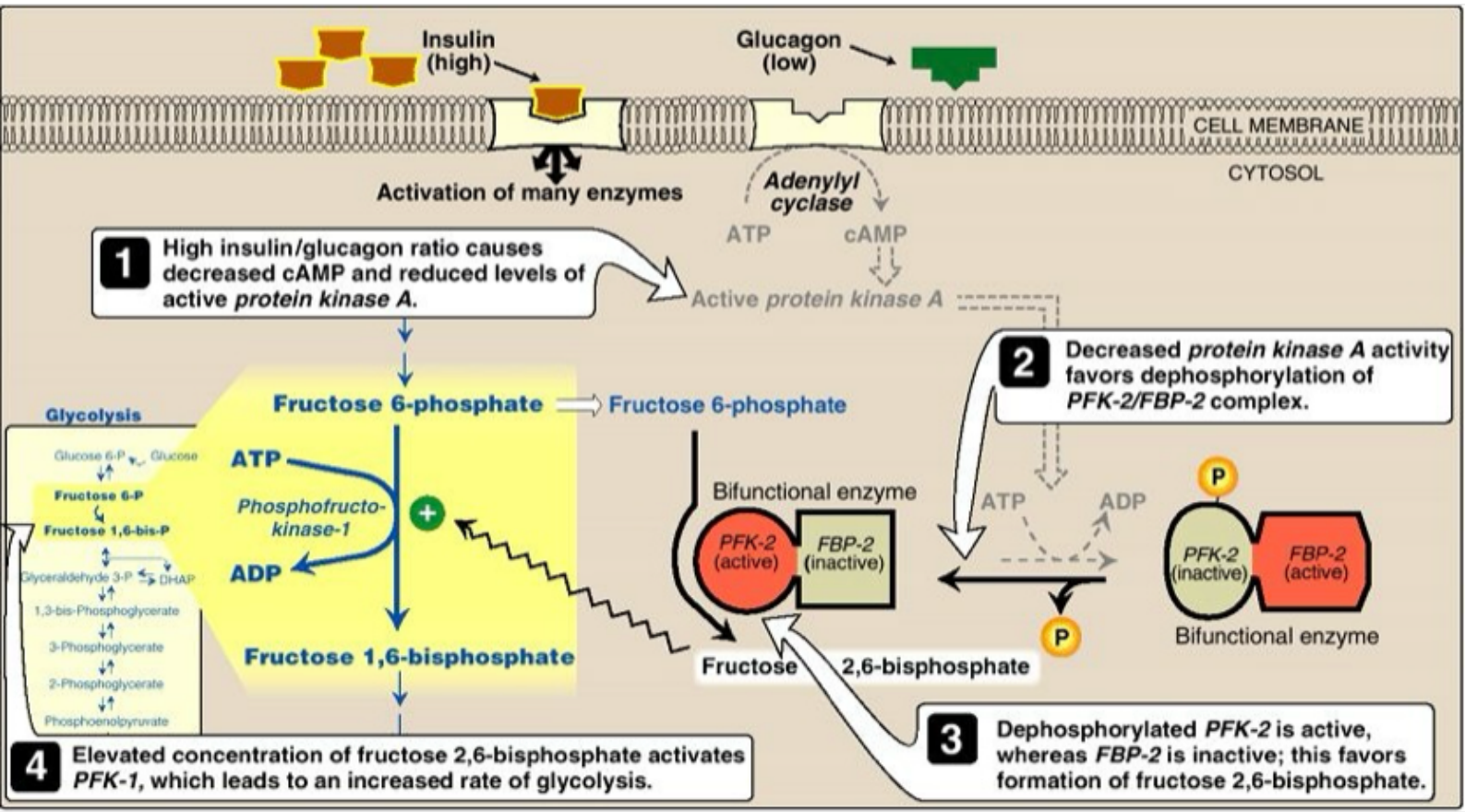


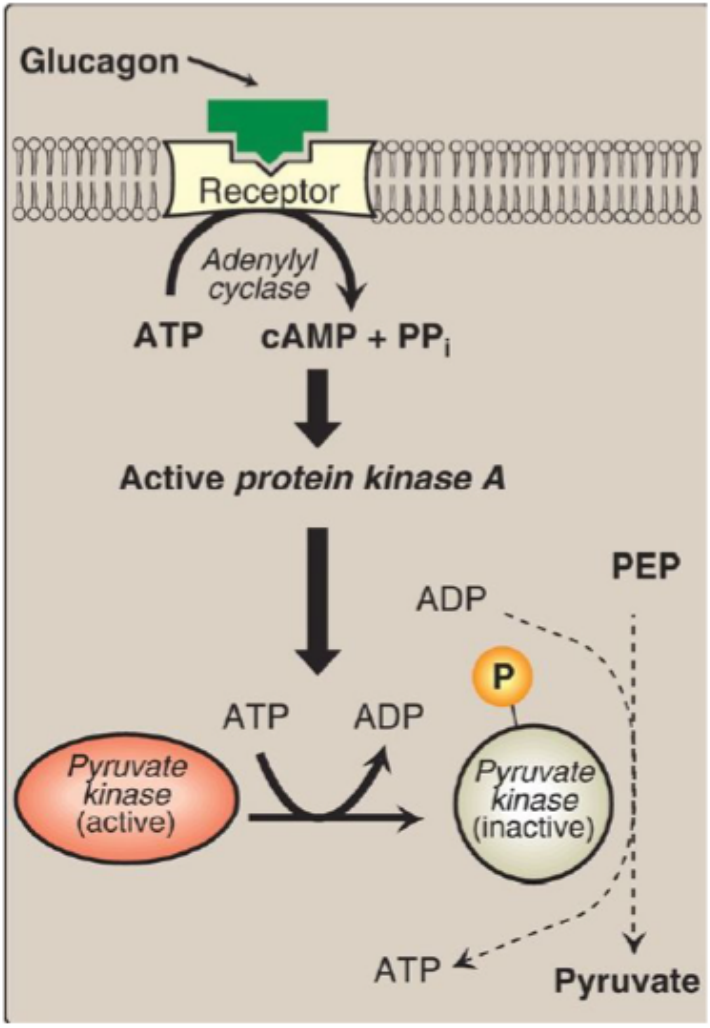
Hormonal regulation of Glycolysis

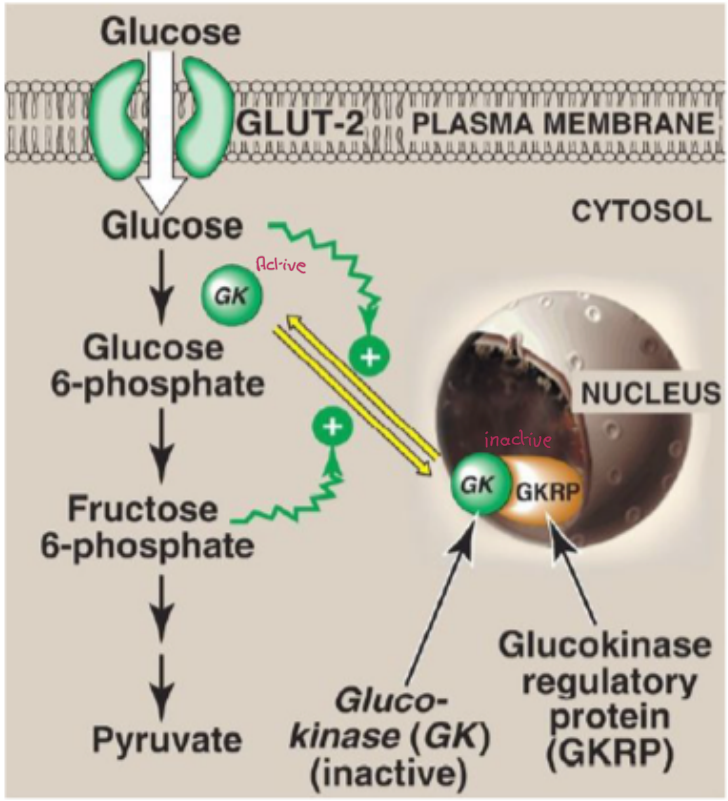
- GK (or HK), PFK and PK are the key enzymes of glycolysis.
- PFK is the most important and considered the rate limiting enzyme.
- Hormones regulate glycolysis according to blood glucose level:
  - After CHO feeding: blood glucose increases, this stimulates insulin secretion, insulin stimulates glycolysis by increasing the synthesis of the three key enzymes: GK, PFK and PK.
  - During fasting: blood glucose level decreases, which inhibits insulin secretion and stimulates glucagon, adrenaline and corticosteroid which inhibit the synthesis of and activity of GK, PFK anc PK.






Insulin (high)
Glucagon (low)
CELL MEMBRANE
CYTOSOL
Activation of many enzymes
Adenylyl cyclase
ATP
cAMP
1 High insulin/glucagon ratio causes decreased cAMP and reduced levels of active protein kinase A.
Active protein kinase A
2 Decreased protein kinase A activity favors dephosphorylation of PFK-2/FBP-2 complex.
Glycolysis
Glucose 6-P
Glucose
Fructose 6-P
Fructose 1,6-bis-P
Glyceraldehyde 3-P
DHAP
1,3-bis-Phosphoglycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
Fructose 6-phosphate
Fructose 6-phosphate
ATP
Phosphofructo-kinase-1
ADP
Fructose 1,6-bisphosphate
Bifunctional enzyme
PFK-2 (active)
FBP-2 (inactive)
ATP
ADP
P
PFK-2 (inactive)
FBP-2 (active)
Bifunctional enzyme
P
Fructose 2,6-bisphosphate
3 Dephosphorylated PFK-2 is active, whereas FBP-2 is inactive; this favors formation of fructose 2,6-bisphosphate.
4 Elevated concentration of fructose 2,6-bisphosphate activates PFK-1, which leads to an increased rate of glycolysis.


Glucagon
Receptor
Adenylyl cyclase
ATP
cAMP + PPi
Active protein kinase A
PEP
ADP
P
ATP
ADP
Pyruvate kinase (active)
Pyruvate kinase (inactive)
ATP
Pyruvate


Glucose
GLUT-2
PLASMA MEMBRANE
CYTOSOL
Glucose
Active
GK
Glucose 6-phosphate
NUCLEUS
inactive
GK
GKRP
Fructose 6-phosphate
Pyruvate
Gluco-kinase (GK) (inactive)
Glucokinase regulatory protein (GKRP)

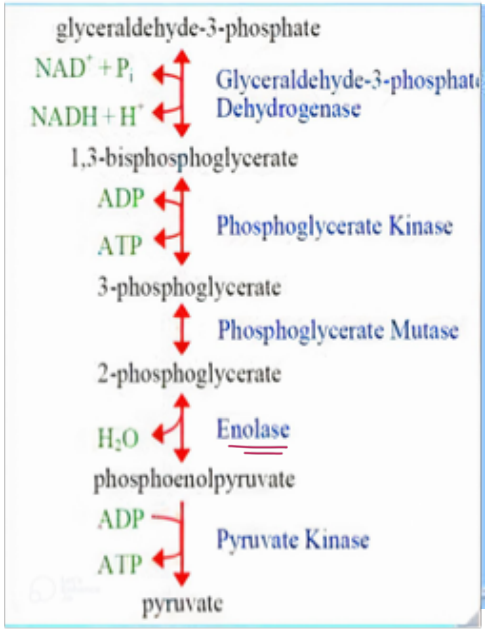
معلومه كالماشي

بالمختبر

In-vitro inhibition of glycolysis

- Flouride inhibits enolase enzyme (step 8)
  - It is used in toothpastes as it inhibits glycolysis in mouth bacterial flora.
  - It is also used as anticoagulant for blood samples to estimate its glucose content.

تقيير



صيك خلصنا الـ Glycolysis

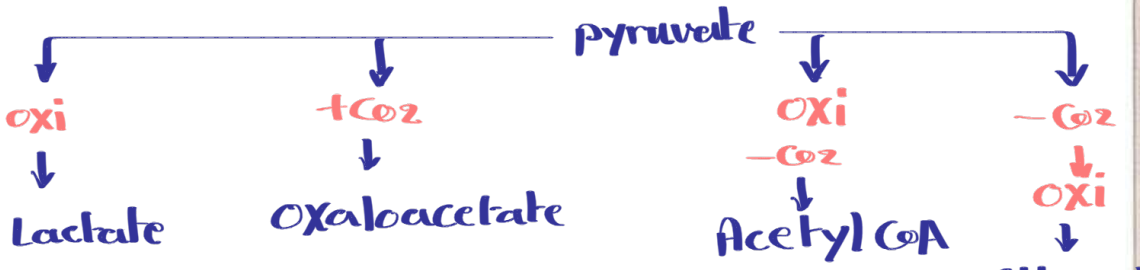
تحلل غلوكوز لـ 2 pyruvat

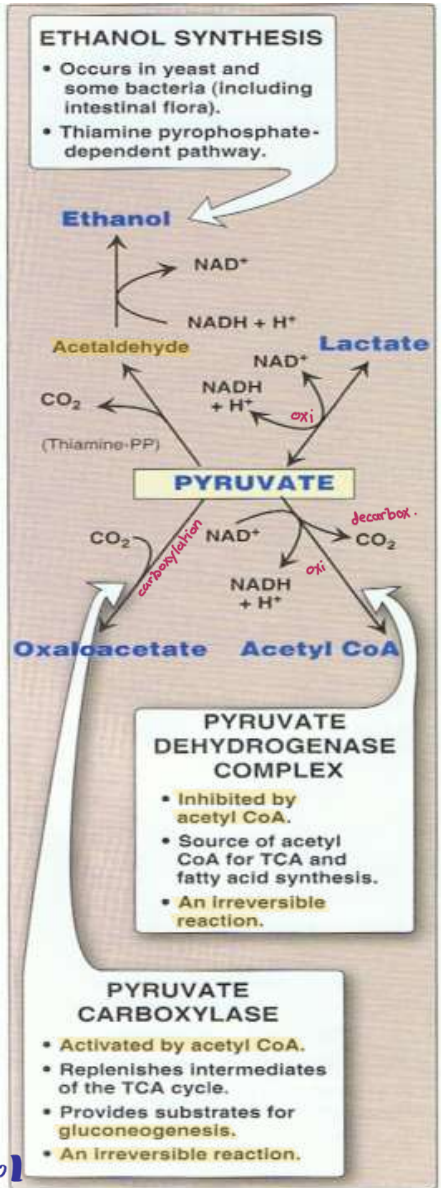
مقدمة للموضوع الجديد

Fate of pyruvic acid

majority → Formation of acetyl CoA

- Formation of oxaloacetic acid → mediator of citric acid cycle
- Formation of lactate → في حالة نقص الـ O_2
- Formation of ethanol (in yeast and some M.O) خميره

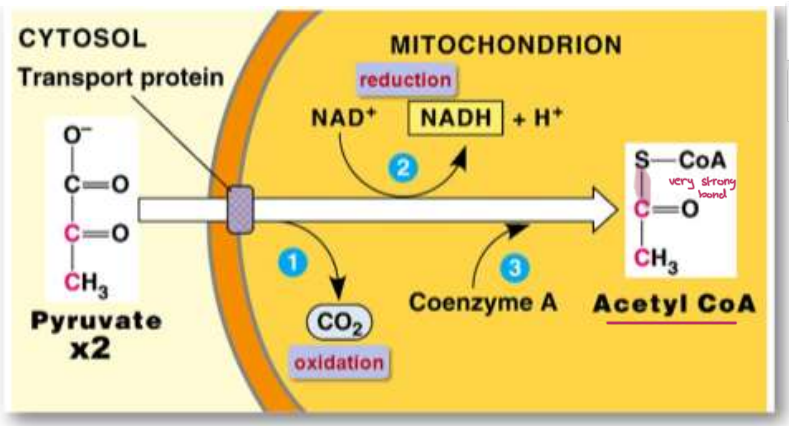




- Needs pyruvate dehydrogenase (PDH) complex
  - Requires 5 coenzymes
    - Thiamine pyrophosphate
    - 2-lipoic acid
    - CoA-SH
    - FAD
    - NAD^+

Aerobic phase of glucose oxidation

- Pyruvic acid formed by glycolysis enters the mitochondria where:
  - it will be metabolized to acetyl-CoA by oxidative decarboxylation and
  - then Acetyl-CoA is oxidized in Kreb's cycle

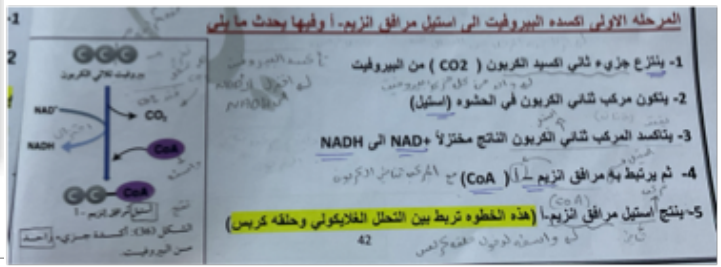


Yield = 2C compound + CO_2 + NADH x2

- Occurs in mitochondria
- Irreversible

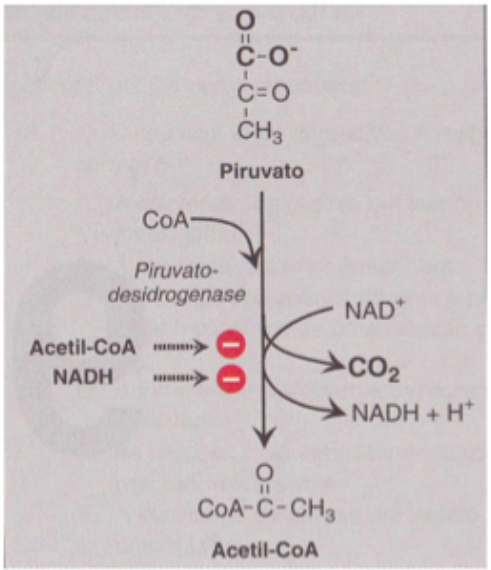
Kreb's cycle → 2 CO_2 + 10 ATP

10 ATP = 2 NADH



Regulation of pyruvate dehydrogenase (PDH)

Directly



By:

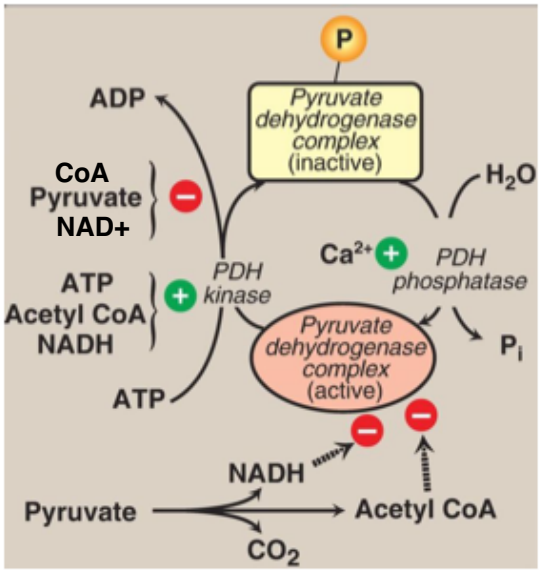
① Acetil-CoA ⊖

② NADH ⊖

] نواتج الـ Dehydrogenation نفسها

* تراكم نواتج أي كعليه يثبطوا العمليه نفسها

indirectly



مباشر

① protein kinase (PDH kinase) → phosphorylate (inactivate) of PDH

② phospho protin phosphatase (PDH phosphatase) → Dephosphrylate (activate) of PDH

غير مباشر

protein kinase: ⊕ ATP, Acetyl CoA, NADH ⊖ CoA, pyruvate, NAD+

phosphoprotin phosphatase: ⊕ Ca^{++} ⊖ NADH, Acetyl CoA

C

Tricarboxylic acid (TCA) cycle

1. Tricarboxylic acid (TCA) cycle is also called citric acid cycle or Kreb's cycle
2. Occurs in the mitochondria of each cell
3. Does not occur in RBCs (no mitochondria)
4. Considered the final common pathway for the complete oxidation of acetyl-CoA obtained from partial oxidation of CHO, lipids and proteins. → here we finish the cellular respiration

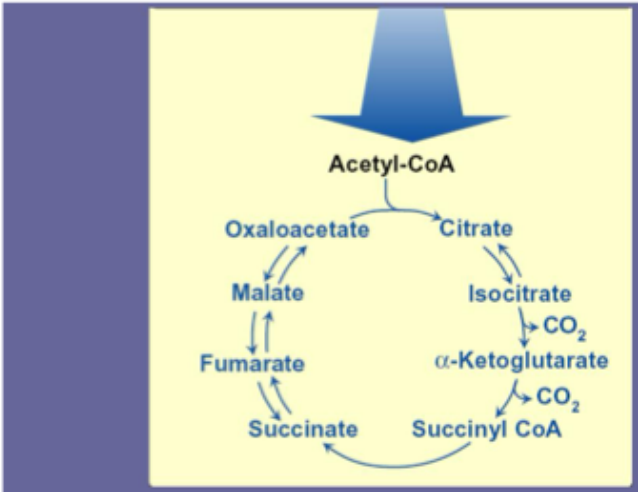


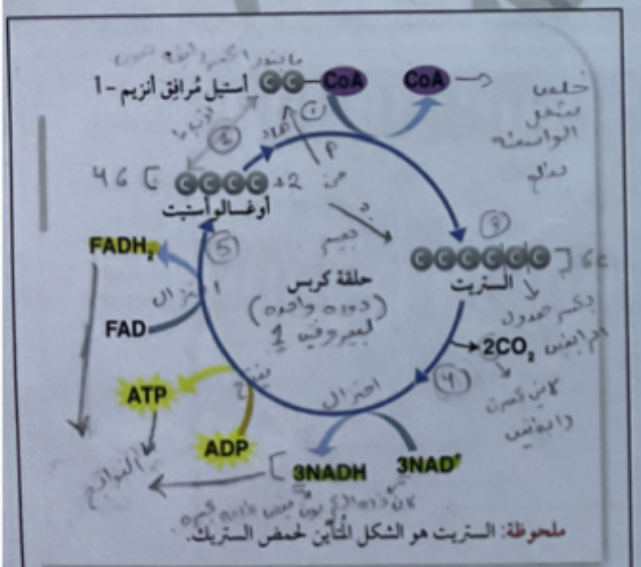
Figure 9.1. The tricarboxylic acid cycle shown as a part of the central pathways of energy metabolism.

مراحل حلقه كريبس

1- تبدا حلقه كريبس بتفاعل استيل مرافق انزيم-أ ثنائي الكربون مع مركب رباعي الكربون يسمى اوغسالواستيت

2- ينتج من هذا التفاعل الستريت (الستريت هو الشكل المتأين لحمض الستريك)وهو مركب سداسي الكربون

3- يدخل الستريت في سلسله من التفاعلات يفقد خلالها جزيئيي ثاني اكسيد الكربون (CO_2) ليعاد انتاج مركب اوغسالواستيت



الشكل (37): حلقة كريس لدورة واحدة. أحدِّد نواتج دورتي حلقة كريس.

ماذا يحدث خلال التفاعلات في حلقه كريبس

1- تختزل ثلاثه جزيئات من +NAD الى NADH

2- يختزل جزيء واحد من FAD الى $FADH_2$

ينتج جزيء واحد من ATP بصوره مباشره

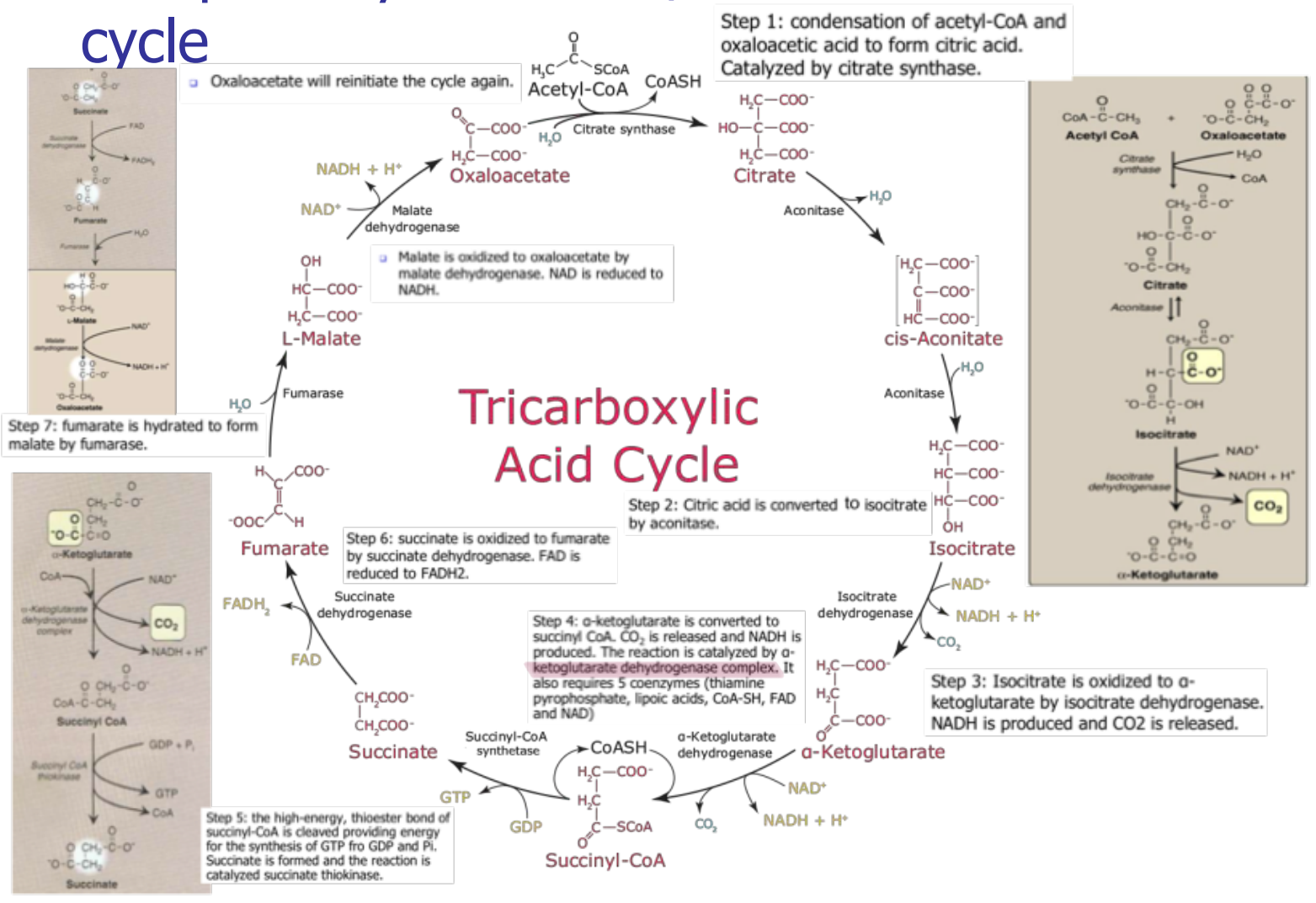
ملاحظه يجب ان تتم دورتان من حلقة كريس لكل جزيء غلوكوز .

(1ATP / 1FADH2 / 3NADH / 2CO2)

(×2) :

(2ATP / 2FADH2 / 6NADH / 4CO2)

Complete cycle of TCA/citric acid or kreb's cycle



Energy gain in Kreb's cycle

Isocitrate DH	1 NADH	2.5 ATP
α-ketoglutarate	1 NADH	2.5 ATP
Succinate thiokinase	1 GTP	1 ATP
Succinate DH	1 FADH2	1.5 ATP
Malate DH	1 NADH	2.5 ATP
Net gain		**10** ATP

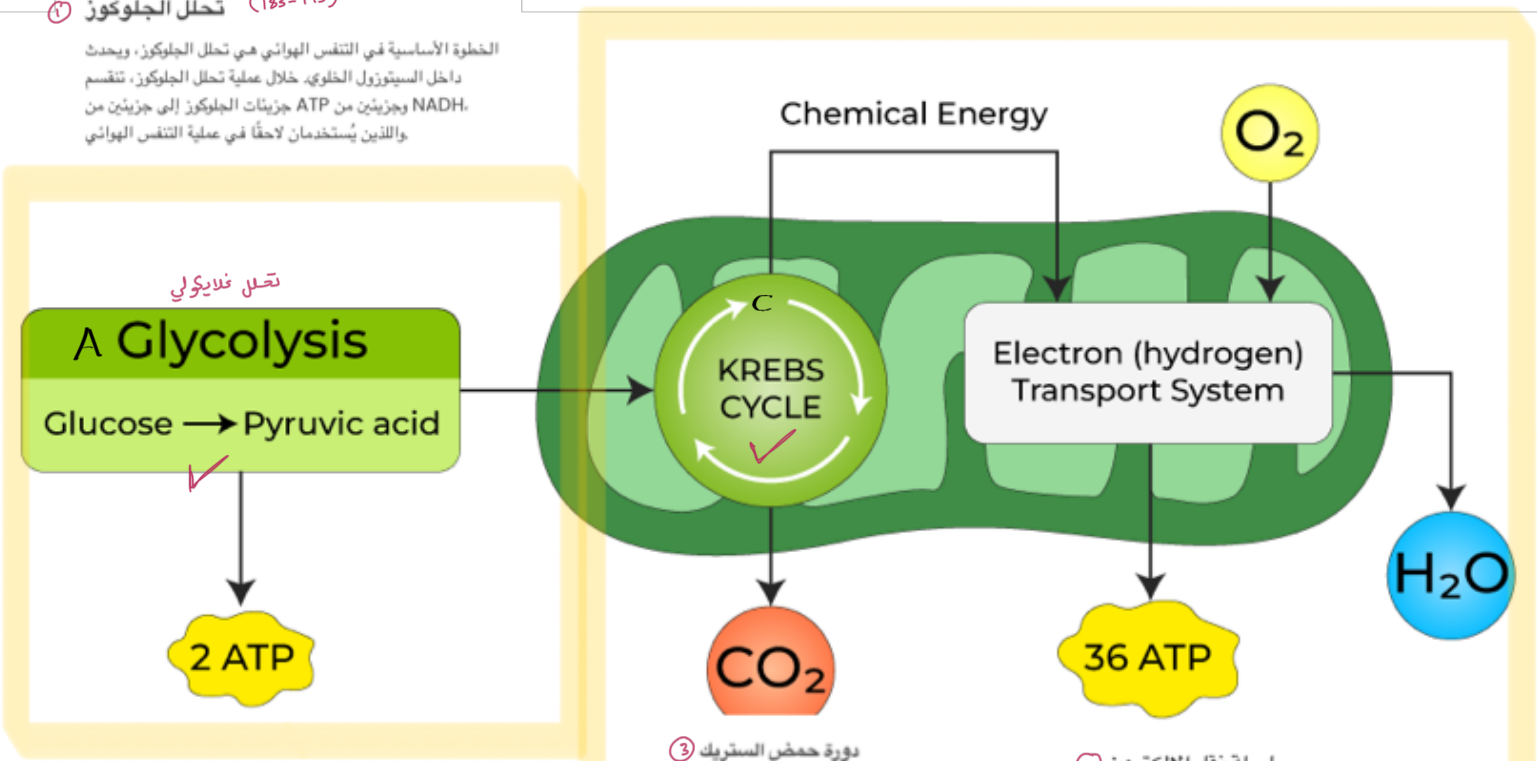
1) Cellular respiration

خطوات التنفس الهوائي

يتم عملية التنفس الهوائي بالكامل في أربع مراحل مختلفة

① تحلل الجلوكوز (188-195)

الخطوة الأساسية في التنفس الهوائي هي تحلل الجلوكوز، ويحدث داخل السيتوزول الخلوي. خلال عملية تحلل الجلوكوز، تنقسم جزيئات الجلوكوز إلى جزيئين من ATP وجزيئين من NADH، واللذين يُستخدمان لاحقًا في عملية التنفس الهوائي.



② تكوين أسيتيل مرافق الإنزيم أ B

الخطوة الثانية في التنفس الهوائي هي تكوين أسيتيل مرافق الإنزيم أ. في هذه العملية، يتأكسد البيروفات في الميتوكوندريا، وتنتج مجموعة أسيتيل ثنائية الكربون. ترتبط مجموعة الأسيتيل ثنائية الكربون الناتجة حديثًا مع مرافق الإنزيم أ، منتجةً أسيتيل مرافق الإنزيم أ. (197 /198)

③ دورة حمض الستريك

الخطوة الثالثة في التنفس الهوائي هي دورة حمض الستريك، والتي تُسمى أيضًا دورة كريبس. في هذه المرحلة من التنفس الهوائي، يتحد أوكسالوأسيتات مع أسيتيل مرافق الإنزيم أ، مُنتجًا حمض الستريك. تخضع دورة حمض الستريك لسلسلة من التفاعلات، وتُنتج أساسًا ATP، جزيئين من ثاني أكسيد الكربون، وجزيء واحد من NADH وFADH مُختزلة من (199 – 202)

④ سلسلة نقل الإلكترون

هذه هي الخطوة الأخيرة في التنفس الهوائي. في هذه المرحلة، تُنتج NADH بنقل الإلكترونات من ATP كميات كبيرة من جزيئات FADH. يُنتج جزيء واحد من الجلوكوز ما مجموعه 34 جزيئًا من ATP.

The overall energy gain of glucose oxidation

- Glycolysis --------- 7 ATP + 2 pyruvate
- 2 pyruvate -------- 2 acetyl-coA + 2 NADH ----- 5 ATP
- 2 acetyl CoA --------- 20 ATP
- The net ATP produced by the oxidation of 1 mol of glucose = 32 ATP

آخر معلومة كيمياء

Defects in Glycolysis A

- **Pyruvate dehydrogenase deficiency:** leads to congenital lactic acidosis. → can't make acetyl CoA so our body use: lacte acid pathway
- This enzyme deficiency results in an inability to convert pyruvate to acetyl CoA, causing pyruvate to be shunted to lactic acid via lactate dehydrogenase.
- This causes particular problems for the brain, which relies on the TCA cycle for most of its energy, and is particularly sensitive to acidosis.

1

2

Energy metabolism cycles

Energy metabolism is the process of generating energy (ATP) from nutrients, starts by glycolysis and ends with oxidative phosphorylation

1) Catabolism: cellular respiration **2) Anabolism: Gluconeogenesis**

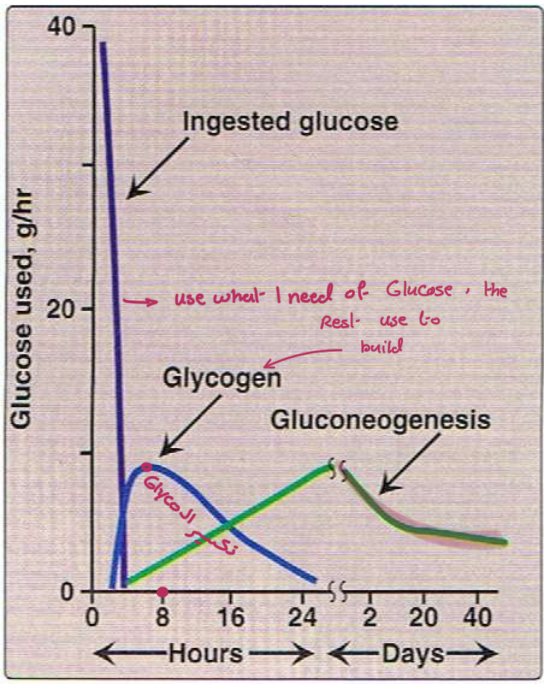
2) Anabolism: Gluconeogenesis

Gluconeogenesis

gluconeogenesis is the synthesis of glucose from non-carbohydrate sources and occurs in liver and kidneys. → stimulated by glucagon

Gluconeogenesis
When and where does it occur

- gluconeogenesis is the synthesis of glucose from non-carbohydrate sources and occurs in liver and kidneys.
- Glucose is formed from precursors as lactate, pyruvate, glycerol and ketoacids
- During prolonged fast and depletion of hepatic glycogen
- During overnight fast, liver is responsible for the majority of gluconeogenesis (90%) and the rest in the kidney
- During prolonged fast, kidney produces about 40% of glucose production.



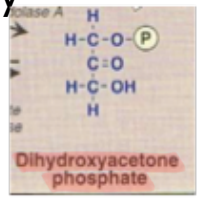
Substrates for gluconeogenesis

- Those include all the intermediates of glycolysis and the citric acid cycle.

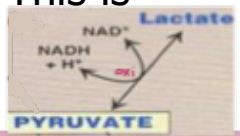
1. Glycerol: released during the hydrolysis of triglycerols in adipose tissue and delivered to the liver. Glycerol is phosphorylated by glycerol kinase to glycerol 3-phosphate, which is oxidized by glycerol 3-phosphate dehydrogenase to dihydroxyacetone phosphate which is an intermediate of glycolysis.

Fate: always delivered to the liver EXCLUSIVLY

glycerol —(glycerol kinase, phosphorylation)→ glycrol-3-phosphate —(oxidation by glycerol phosphol. dehydrogenase)→ Dihydroxy acetone phosphate



2. Lactate: released by exercising muscles and RBC's. This is transferred to the liver and reconverted to glucose.



3. Amino acids: hydrolysis of tissue proteins are the major source of glucose. α-ketoacids (oxaloacetate and α-ketoglutarate are derived from the metabolism of glucogenic aa which can enter the TCA

product of gluconegenic aa break down

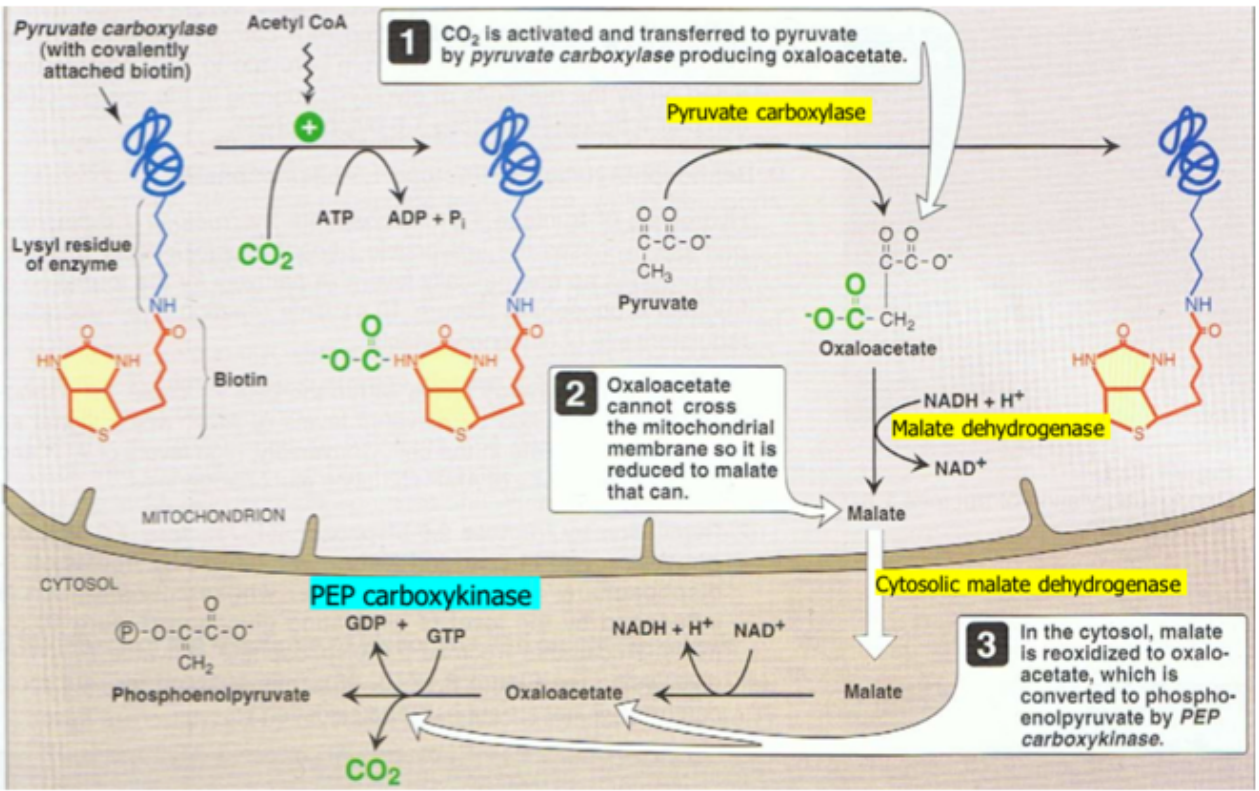
aa — ketogenic
aa — glucogenic → gluconegenesis → Glucose

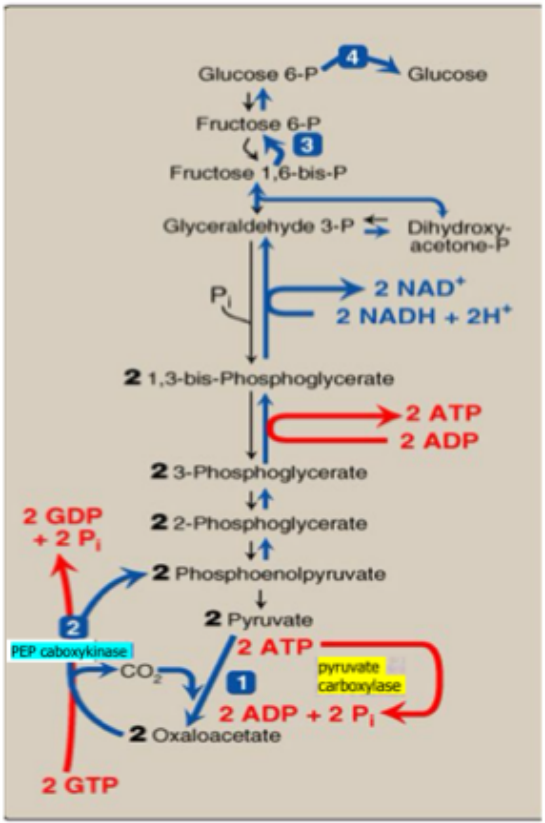
Reactions unique to gluconeogenesis

Seven of the glycolysis reactions are reversible and are used for gluconeogensis while three of them are irreversible (Pyruvate kinase, phosphofructokinase and hexokinase)

my problem

Pyruvate carboxylase: Pyruvate is converted to phosphoenolpyruvate (PEP) by pyruvate carboxylase and PEP caboxykinase





1 Pyruvate carboxylase

A specific enzyme of gluconeogensis to solve the irreversible problem

* Lactate → Liver → pyruvate → oxaloacetate

هاي باختصار الي بعملو عاد الانزيم

Pyruvate carboxylase :

it's Co-enzyme

Biotin: covalently bound to the N of lysine in the pyruvate carboxylase, requires CO_2 and ATP for the convertion of pyruvate to oxaloacetate. It occurs in mitochondria of liver and kidney. Muscles contain also pyruvate carboxylase for the use of OAA in TCA.

controlled by

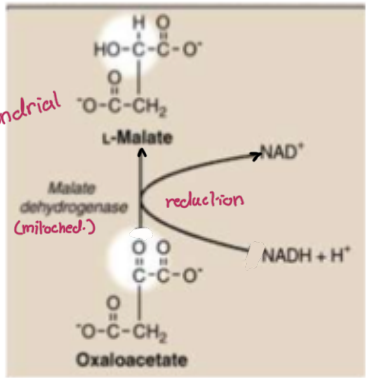
Allosteric regulation: it is allosterically activated by Acetyl coA. → came from lipids metabolism not glycolysis

إذا أول مرحلة نتج منها oxaloacetate
بس السؤال شو بدي أعمل فيه لسا ما
صنعت phosphoenolpyruvate

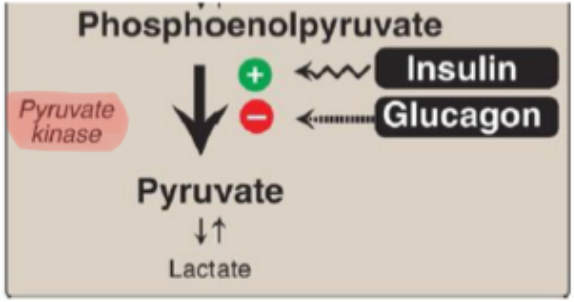
2 PEP caboxykinase

2. Transport of oxaloacetate to the cytosol: oxaloacetate can't cross the ① mitochondrial membrane so it is reduced to malate by malate dehydrogenase that can cross. In cytosol malate is reoxidized to oxaloacetate by cytosolic malate dehydrogenase. ② → cytolic

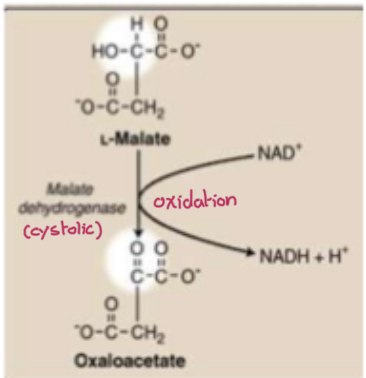
3. Oxaloacetate is decarboxylated and phosphorylated in the cytosol by PEP carboxykinase which utilize 1 GTP.



mitochondrial



إذا أنا قدرت ارجع pyruvate الى phosphoenolpyruvate
باستخدام انزيمين:
1) pyruvate carboxylase
2) PEP carboxykinase



ENTJ istp ENTP ISTP INTJ

pyruvate kinase is irreversible يعني كلها هاي الميمعه عشان ال

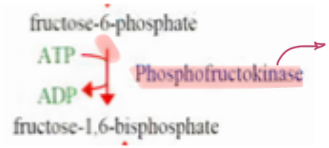
هاد المقصود ب

Pyruvate carboxylase: Pyruvate is converted to phosphoenolpyruvate (PEP) by pyruvate carboxylase and PEP caboxykinase

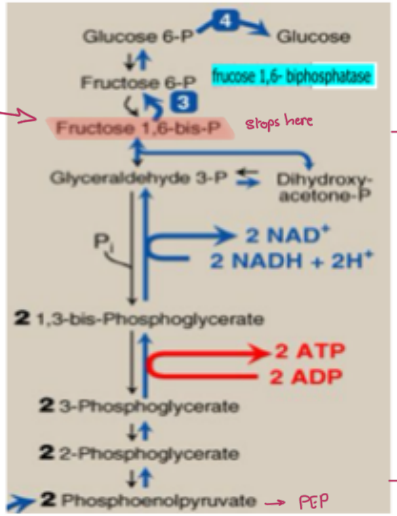
بعدين

Phosphoenolpyruvate (PEP) will continue in the reverse of glycolysis until reach fructose 1,6- biphosphate.

*PEP will continue in the reverse of glycolysis until reach fructose 1,6- biphosphate.



irreversable → so we use new enzyme: frucose 1,6- biphosphatase



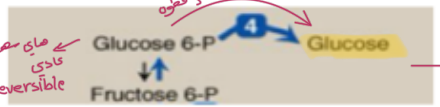
reversabile processes and enzymes

4. Dephosphorylation of frucose 1,6- biphosphate by frucose 1,6- biphosphatase to produce fructose 6-phosphate will bypass the irreversible PFK reaction.

مهم The enzyme is inhibited by high levels of AMP (I need ATP) and fructose 2,6- biphosphate, while high level of ATP and low AMP stimulate gluconeogenesis

means high ATP

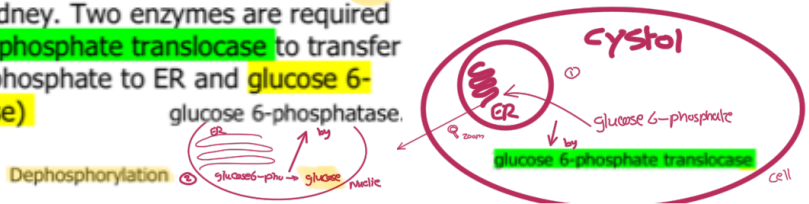
Then: يعني آخر فوايده



صار صعب عادي reversible

we use: glucose 6-phosphate translocase, glucose 6-phosphatase

5. Dephosphorylation of glucose 6-phosphate: occurs by glucose 6-phosphatase. This occurs only in liver and kidney. Two enzymes are required (glucose 6-phosphate translocase to transfer glucose 6-phosphate to ER and glucose 6-phosphatase)



Notes:

يعني أنا هسا الغلوكوز صفّا مخزن بال ER طيب لما أحتاجه وآجي أطلعه إلى ال cyctol مين بطلعو؟

الجواب * Glute-7

* Glute-2 → very imp in gluconeogenesis in liver and kidney → why?

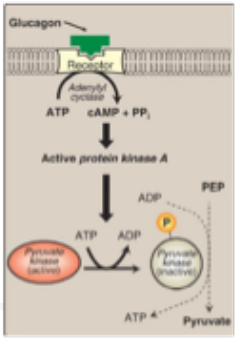
→ Bc I need it in transport the glucose synthesised in these organs to the blood stream when needed

Type 1a glycogen storage disease results from inherited diffeciency of one of them which has the following symptoms:

- Hypoglycemia
- Hepatomegaly and liver problems
- Lactic acidosis
- Growth failure

glucose 6-phosphate translocase
glucose 6-phosphatase

Regulation of gluconeogenesis

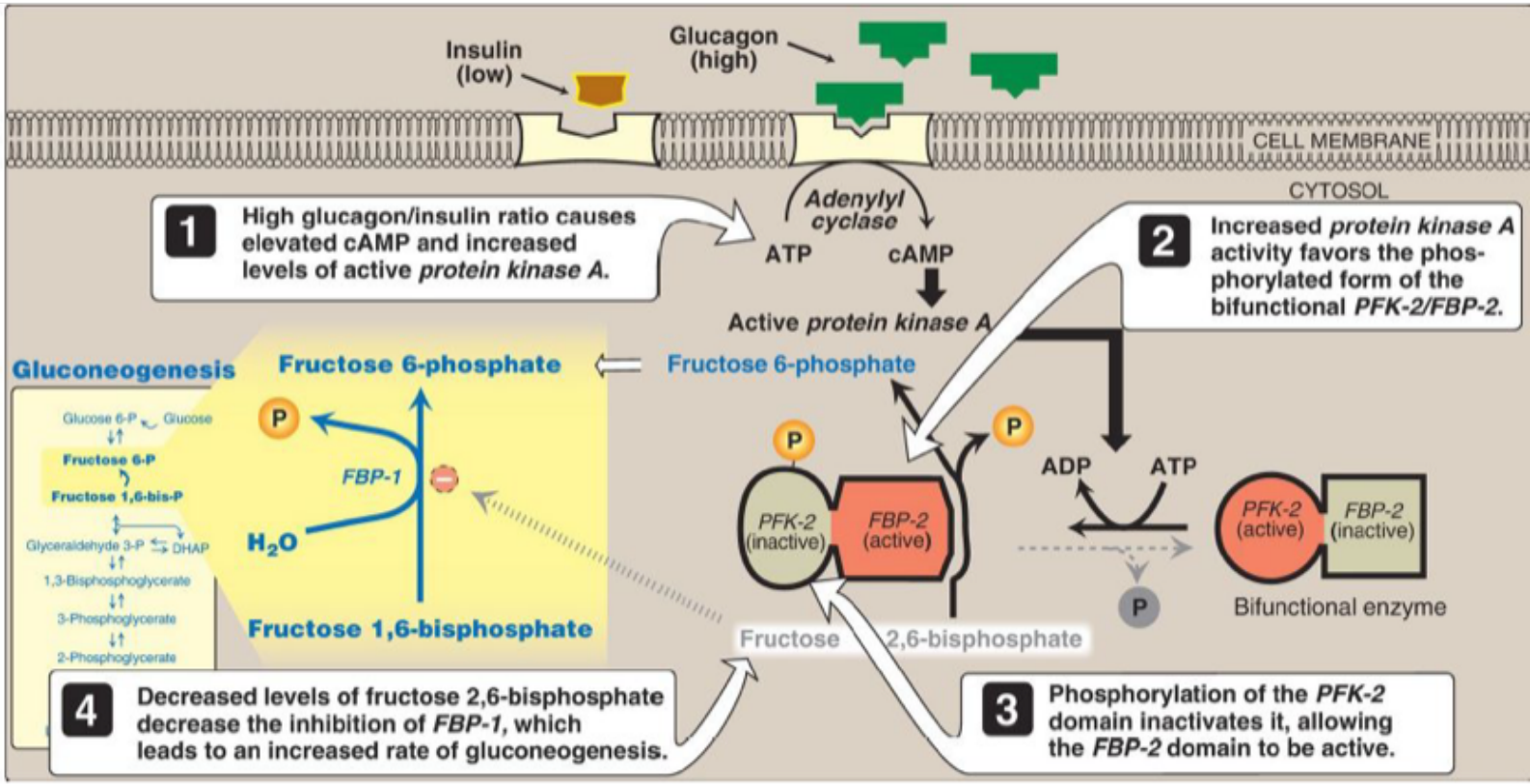


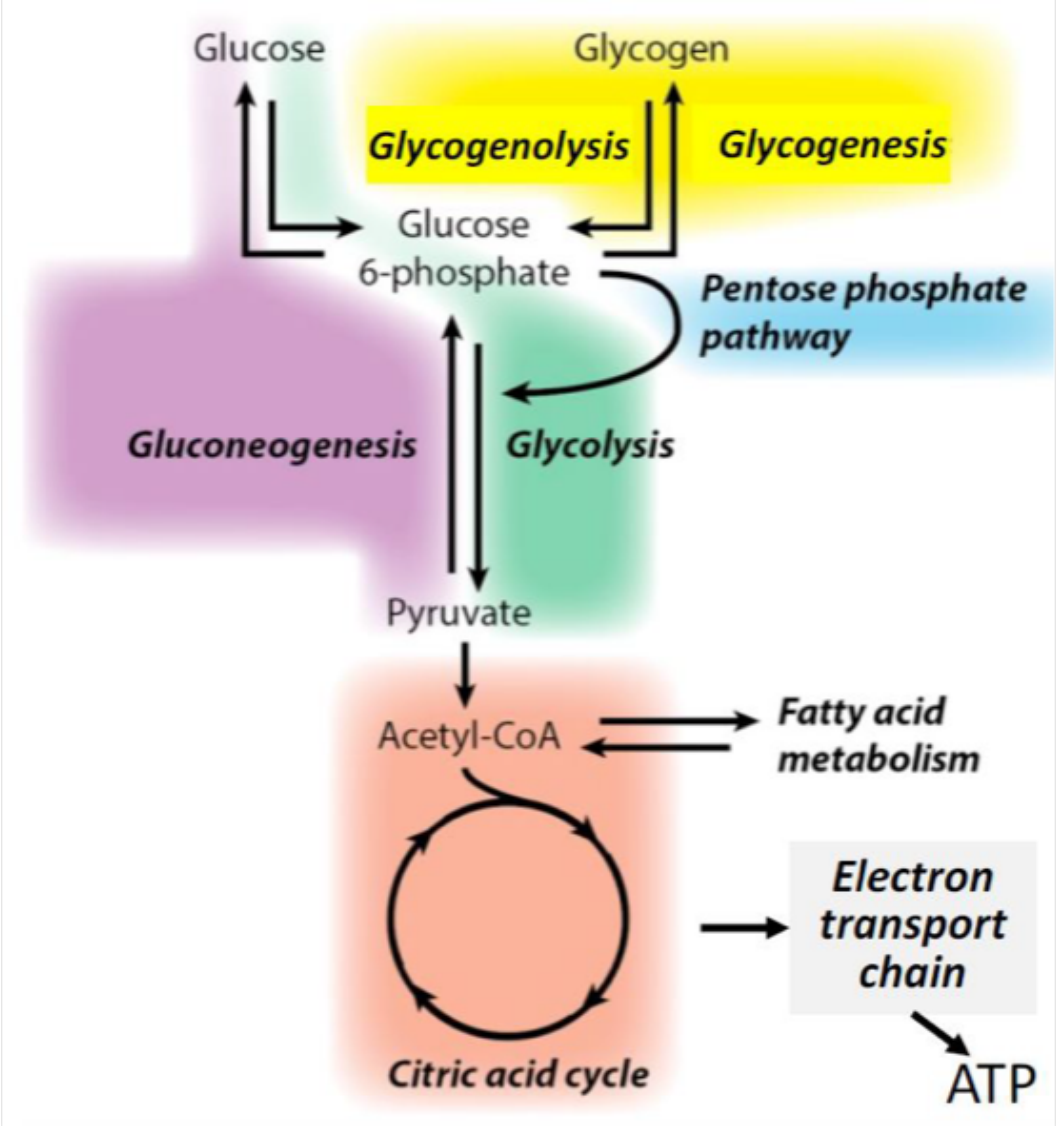
hormone

1. Glucagon: stimulates gluconeogenesis in three mechanisms:
    1. **Change in allosteric effectors:** it lowers level of fructose 2,6-biphosphate leading to activation of fructose 1,6-biphosphatase and inhibition of phosphofructokinase.
    2. **Covalent modification of enzyme activity:** it elevate cAMP leading to activation of cAMP-dependent protein kinase activity which will phosphorylate pyruvate kinase to its inactive form.
    3. **Induction of enzyme synthesis:** it increases the transcription of PEP carboxykinase gene.
2. Substrate availability: like glucogenic amino acids
3. Allosteric activation of pyruvate carboxylase by acetyl coA.
4. Allosteric inhibition of fructose 1,6-bisphosphatase by AMP

Note: ATP and NADH are produced in large quantities during fasts from fatty acid oxidation is required for gluconeogenesis.

Glucagon stimulates gluconeogenesis

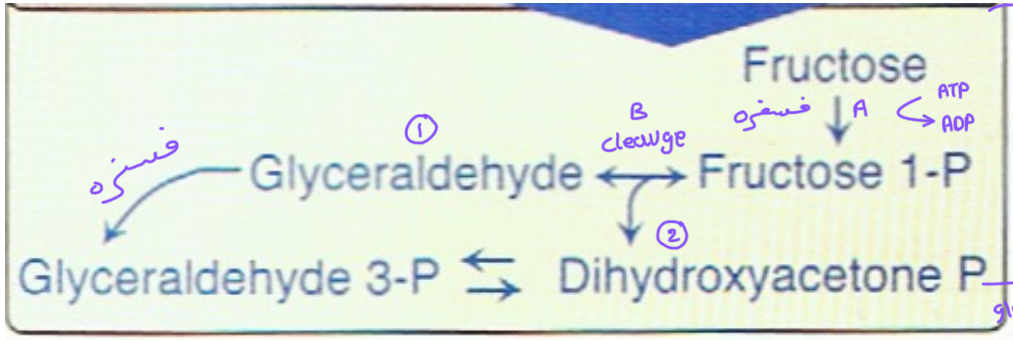



Glucose
Glycogen
Glycogenolysis
Glycogenesis
Glucose
6-phosphate
Pentose phosphate
pathway
Gluconeogenesis
Glycolysis
Pyruvate
Acetyl-CoA
Fatty acid
metabolism
Electron
transport
chain
Citric acid cycle
ATP

Metabolism of mono and disaccharide

Where do we get the fructose from?

- The major source of fructose is the disaccharide sucrose, which, when cleaved in the intestine, releases equimolar amounts of fructose and glucose
- fructose is also found as a free monosaccharide in high-fructose corn syrup (55 percent fructose/45 percent glucose, which is used to sweeten most cola drinks), in many fruits, and in honey.
- Entry of fructose into cells is not insulin-dependent and, in contrast to glucose, fructose does not promote the secretion of insulin.

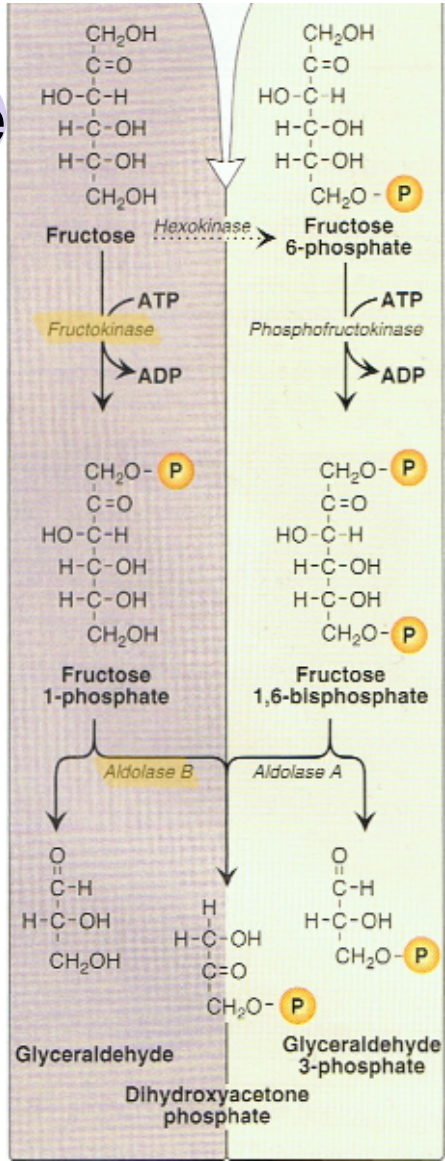


Metabolism of fructose

A. Phosphorylation of fructose: by hexokinase or fructokinase (found in the liver, kidney, and the small intestinal mucosa). and converts fructose to fructose 1-phosphate, using ATP as the phosphate donor

B. Cleavage of fructose 1-phosphate (by aldolase B) to dihydroxyacetone phosphate (DHAP) ① and glyceroldehyde. DHAP can directly enter glycolysis or gluconeogenesis, whereas glyceraldehyde can be metabolized by other pathways

DHAP is an intermediate of both: ②



Metabolism of fructose

العركه داخل الجسم

C. Kinetics of fructose metabolism

A. The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass phosphofructokinase (the major rate-limiting step in glycolysis).

Trioses النواتج فوقه تاعت التكسير

مرّة بطيء

واقفه على عالانزيم

B. Intravenous infusion of fructose elevate the rate of lipogenesis caused by the enhanced production of acetyl CoA.

فش فيجو ؟ تخطي !

lipogenesis → the process in which lipids are produced

إذا إنزيم اللي بيخلي عملية glycolysis بطيئة هو phosphofructokinase بما إنه مش مستخدم لتكسير الفكرتوز اكيد هتكون ال metabolism اسرع بهاي الحاله

الكبدون

D. Disorders of fructose metabolism

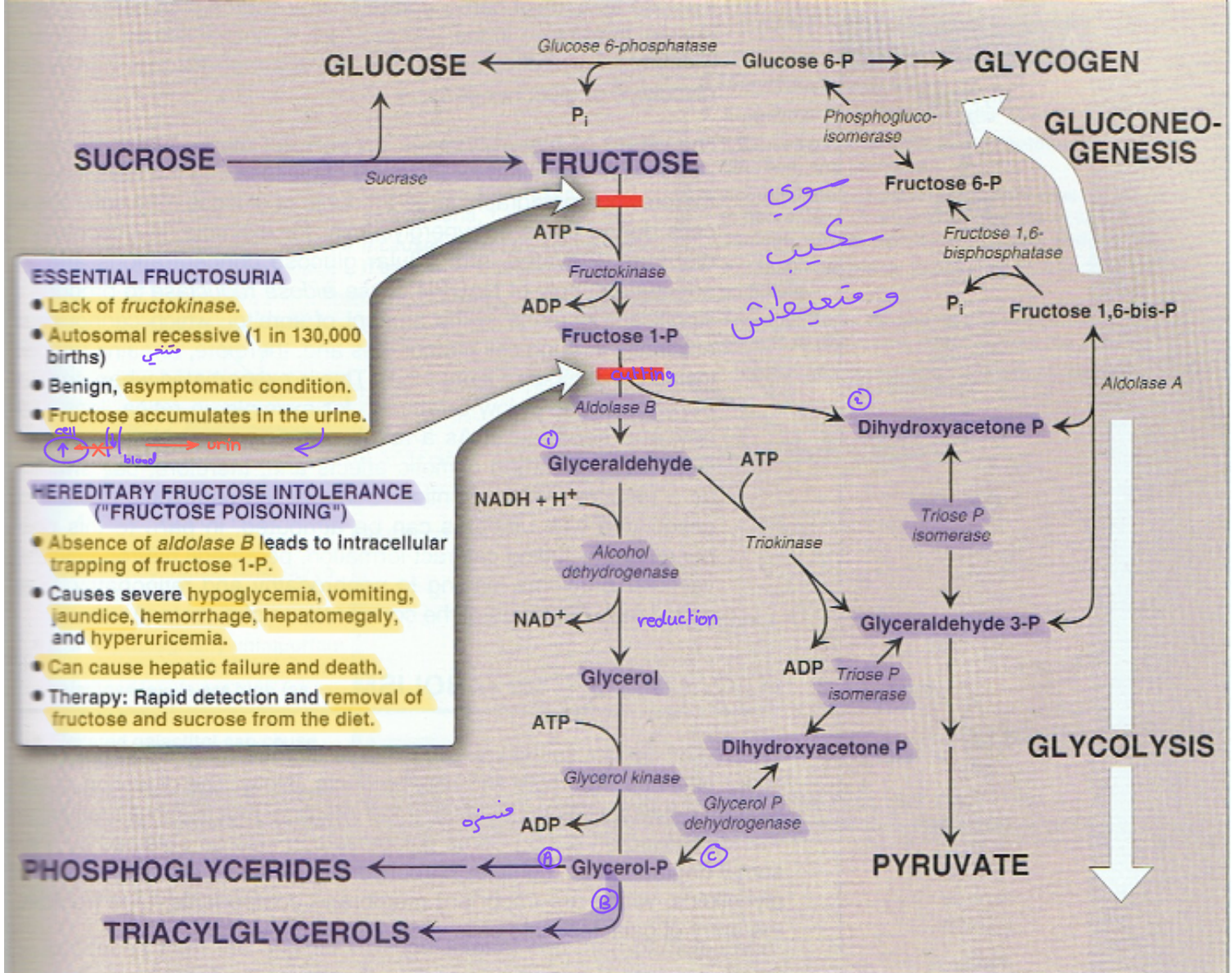
A. fructokinase deficiency: benign condition

مش خطير ← حميد

خطير ← B. Hereditary fructose intolerance (HFI): a severe disturbance of liver and kidney metabolism as a result of aldolase B deficiency. Fructose 1-phosphate accumulates, and ATP ↓ and inorganic phosphate ↓ levels fall significantly, causing hyperuricemia, hypoglycemia, vomiting, jaundice, hemorrhage and hepatomegaly.

If fructose was not removed from the diet, liver failure and death can occur.

Diagnosis of HFI can be made on the basis of fructose in the urine


GLUCOSE
Glucose 6-phosphatase
Glucose 6-P
GLYCOGEN
P_i
Phosphogluco-isomerase
GLUCONEO-GENESIS
SUCROSE
Sucrase
FRUCTOSE
Fructose 6-P
ATP
Fructokinase
Fructose 1,6-bisphosphatase
ADP
P_i
Fructose 1,6-bis-P
Fructose 1-P
Aldolase A
Aldolase B
Dihydroxyacetone P
Glyceraldehyde
ATP
NADH + H^+
Triose P isomerase
Triokinase
Alcohol dehydrogenase
NAD^+
reduction
Glyceraldehyde 3-P
Glycerol
ADP
Triose P isomerase
ATP
Dihydroxyacetone P
GLYCOLYSIS
Glycerol kinase
Glycerol P dehydrogenase
ADP
PHOSPHOGLYCERIDES
Glycerol-P
PYRUVATE
TRIACYLGLYCEROLS
ESSENTIAL FRUCTOSURIA
Lack of fructokinase.
Autosomal recessive (1 in 130,000 births)
Benign, asymptomatic condition.
Fructose accumulates in the urine.
urin
blood
HEREDITARY FRUCTOSE INTOLERANCE ("FRUCTOSE POISONING")
Absence of aldolase B leads to intracellular trapping of fructose 1-P.
Causes severe hypoglycemia, vomiting, jaundice, hemorrhage, hepatomegaly, and hyperuricemia.
Can cause hepatic failure and death.
Therapy: Rapid detection and removal of fructose and sucrose from the diet.

Metabolism of fructose

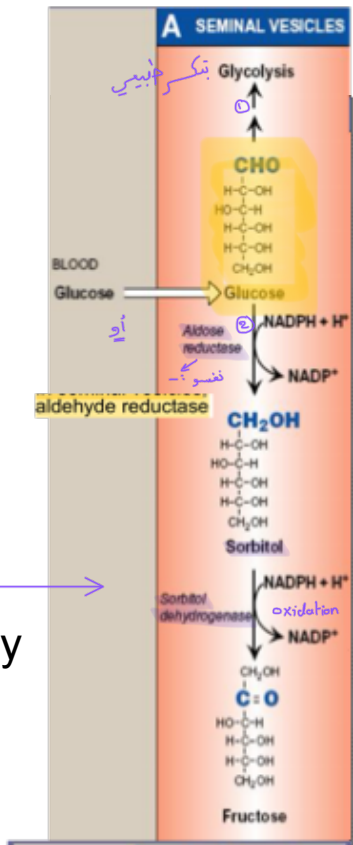
E. Conversion of mannose to fructose 6-phosphate

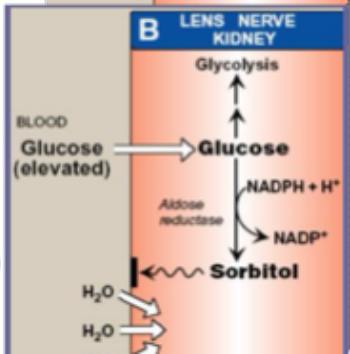
Hexokinase phosphorylates mannose, producing mannose 6-phosphate, which is (reversibly) isomerized to fructose 6-phosphate by phosphomannose isomerase.

F. Conversion of glucose to fructose via sorbitol

A. In seminal vesicles, glucose converts to sorbitol by aldehyde reductase followed by oxidation of sorbitol by sorbitol dehydrogenase to produce fructose. This is necessary in seminal vesicles as fructose is a major carbohydrate energy source.

B. In hyperglycemia as in uncontrolled diabetes glucose enter these cells (retina, lens, kidney, nerve cells) convert to sorbitol which will be trapped inside the cell, leading to water retention due to osmosis. cataract formation, peripheral neuropathy, and vascular problems leading to nephropathy and retinopathy.





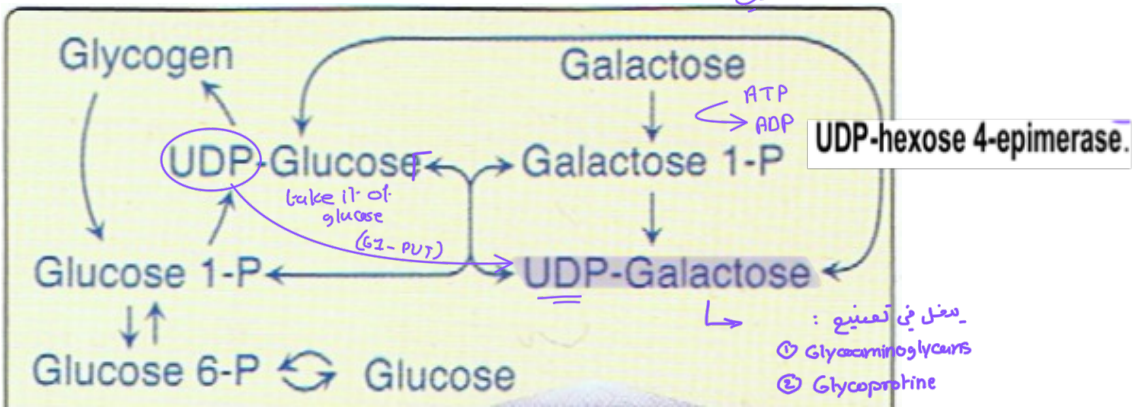
B

Galactose metabolism

- The major dietery source is lactose (in milk)

- ① Phosphorylation of galactose by **galactokinase** to galactose 1P using ATP as phosphate donor

- Formation of UDP-galactose by exchange with UDP-glucose. The enzyme that catalyzes this reaction is **galactose 1-phosphate uridyl-transferase.**



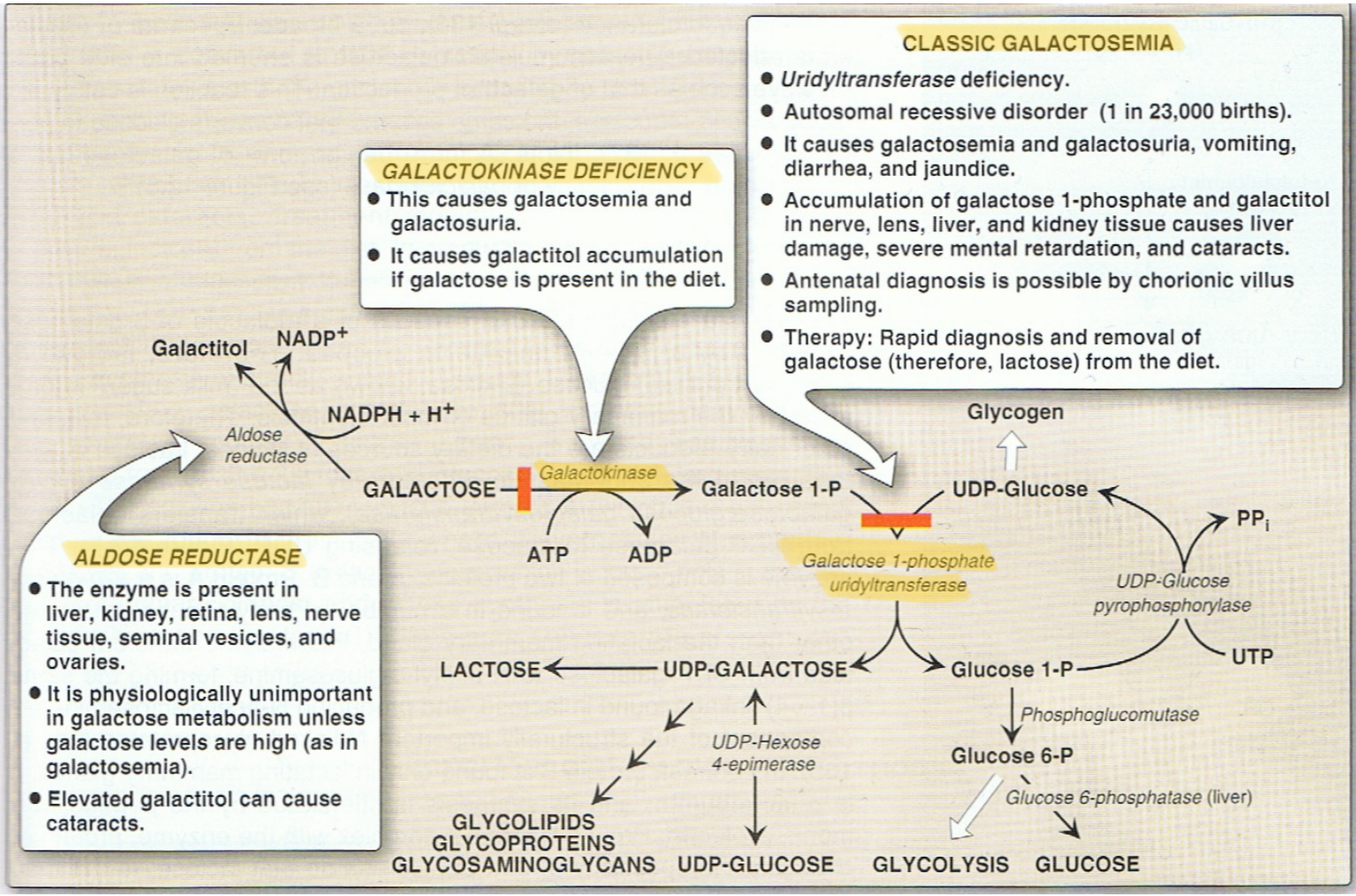
Galactose metabolism

C. Use of UDP-galactose as a carbon source for glycolysis or gluconeogenesis. UDP-galactose is then converted to UDP-glucose by **UDP-hexose 4-epimerase**.

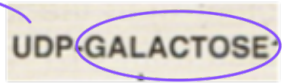
D. Role of UDP-galactose in biosynthetic reactions: can be utilized in many metabolic pathways as in biosynthesis of lactose, glycoproteins, glycolipids, and glycosaminoglycans.

E. Disorders of galactose metabolism

A. classic galactosemia: **Galactose 1-phosphate uridyltransferase** is missing and so galactose 1P and galactose accumulate in cell causing a problem similar to that in fructose intolerance

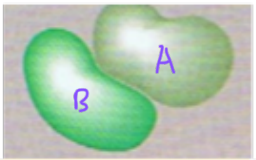

CLASSIC GALACTOSEMIA
• Uridyltransferase deficiency.
• Autosomal recessive disorder (1 in 23,000 births).
• It causes galactosemia and galactosuria, vomiting, diarrhea, and jaundice.
• Accumulation of galactose 1-phosphate and galactitol in nerve, lens, liver, and kidney tissue causes liver damage, severe mental retardation, and cataracts.
• Antenatal diagnosis is possible by chorionic villus sampling.
• Therapy: Rapid diagnosis and removal of galactose (therefore, lactose) from the diet.
GALACTOKINASE DEFICIENCY
• This causes galactosemia and galactosuria.
• It causes galactitol accumulation if galactose is present in the diet.
Galactitol
NADP+
NADPH + H+
Aldose reductase
GALACTOSE
Galactokinase
ATP
ADP
Galactose 1-P
Glycogen
UDP-Glucose
PPi
Galactose 1-phosphate uridyltransferase
UDP-Glucose pyrophosphorylase
UTP
LACTOSE
UDP-GALACTOSE
Glucose 1-P
Phosphoglucomutase
Glucose 6-P
Glucose 6-phosphatase (liver)
UDP-Hexose 4-epimerase
GLYCOLIPIDS
GLYCOPROTEINS
GLYCOSAMINOGLYCANS
UDP-GLUCOSE
GLYCOLYSIS
GLUCOSE
ALDOSE REDUCTASE
• The enzyme is present in liver, kidney, retina, lens, nerve tissue, seminal vesicles, and ovaries.
• It is physiologically unimportant in galactose metabolism unless galactose levels are high (as in galactosemia).
• Elevated galactitol can cause cataracts.

Lactose synthesis



- Produced in mammary glands of mammals
- Lactose is synthesized by lactose transferase which transfers galactose from UDP-galactose to glucose, releasing UDP.
- This enzyme is composed of two proteins, A and B. Protein A is a **β-o-galactosyltransferase**, and is found in a number of body tissues.
- In tissues other than the lactating mammary gland, this enzyme transfers galactose from UDP-galactose to N-acetyl-D-glucosamine, forming the same (1-4) linkage found in lactose, and producing N-acetyllactosamine a component of the structurally important N-linked **glycoproteins**.
- In contrast, protein B is found only in lactating mammary glands. It is **α-lactalbumin**, and its synthesis is stimulated by the peptide hormone, prolactin. Protein B forms a complex with the enzyme, protein A, changing the specificity of that transferase so that lactose, rather than N-acetyllactosamine, is produced.

❑ This enzyme is composed of two proteins, A and B.



lactose transferase

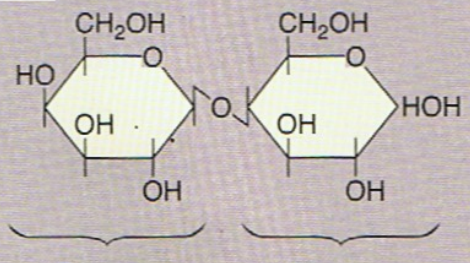
β-D-Galactosyltransferase
(protein A)

α-Lactalbumin
(protein B)

UDP-galactose:glucose
galactosyltransferase

UDP-galactose + glucose → UDP

Lactose



① Protein A is a β-o-galactosyltransferase, and is found in a number of body tissues.

can't be found in

In tissues other than the lactating mammary gland, this enzyme transfers galactose from UDP-galactose to N-acetyl-D-glucosamine, forming the same (1-4) linkage found in lactose, and producing N-acetyllactosamine a component of the structurally important N-linked **glycoproteins**.

protein B is found only in lactating mammary glands.

α-lactalbumin

its synthesis is stimulated by the peptide hormone, prolactin.

Protein B forms a complex with the enzyme, protein A, changing the specificity of that transferase so that lactose, rather than N-acetyllactosamine, is produced.

→ complex formation → lost of specificity → to produce Acetyllactosamine → يصيرو يعملو Lactose

UDP-galactose

β-O-gla...

N-acety-D-glucosamine + galactose

β(1-4)

giving

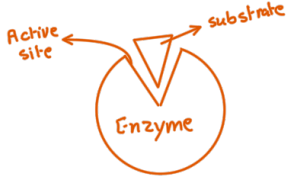
Acetyllactosamine

مكون مهم في N-linked glycoproteins

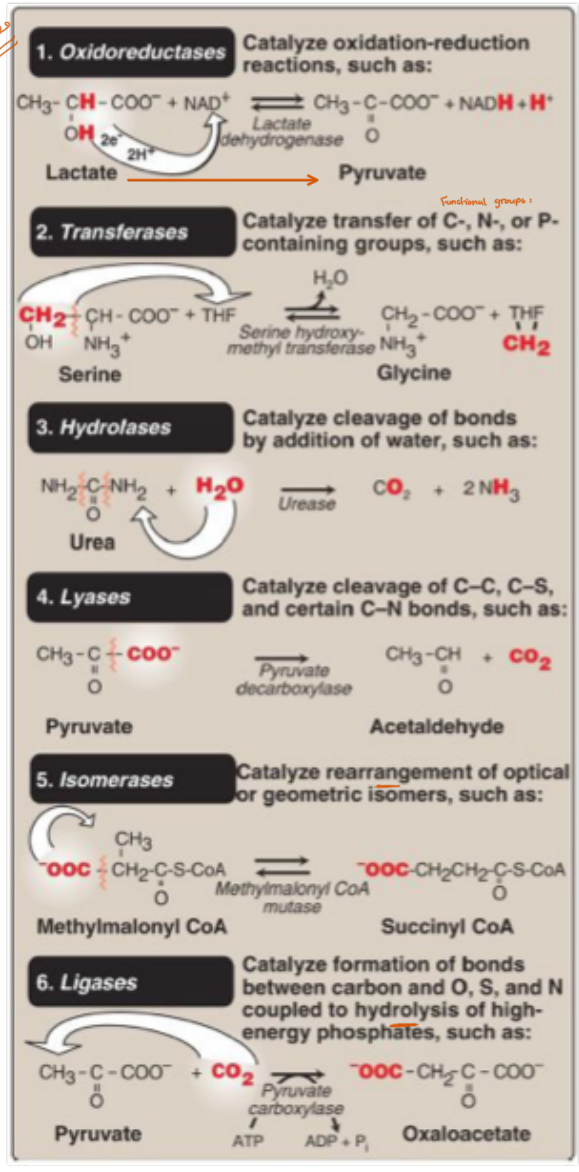
Enzymes

Enzymes

- Enzymes are **protein catalysts** that increase the rate of reactions without being changed in the overall process.



- Nomenclature
  - A. Recommended **name** → according to it's function
    - Most commonly used enzyme names
      - **substrate + -ase** e.g. sucrase, urease, glucosidase)
      - Action performed e.g. lactate dehydrogenase and adenylyl cyclase
  - B. Systematic name
    - IUBMB divided the enzymes into **six major classes**:
      1. **Oxidoreductase**
      2. **Transferase**
      3. **Hydrolases**
      4. **Lyases**
      5. **Isomerases**
      6. **Ligases**
    - Example: lactate:NAD+ oxidoreductase



Enzyme properties

1. Active sites: enzyme contain special pocket or cleft that binds the substrate

2. Catalytic efficiency: highly efficient (10^3-10^8) faster than uncatalyzed reaction

3. Specificity: highly specific, catalyzes only one type of chemical reactions.

4. Cofactors, Apoenzyme and holoenzyme: some enzymes need nonprotein **cofactors** like metal or organic molecule. The enzyme with cofactor is called **holoenzyme**, the protein portion is **apoenzyme**. The enzyme without cofactor doesn't show biological activity

5. Regulation: can be activated or inhibited by different substances.

6. Location within the cell: each enzyme is localized in specific organelle within the cell which isolates the reaction substrate or product from other competing reactions.

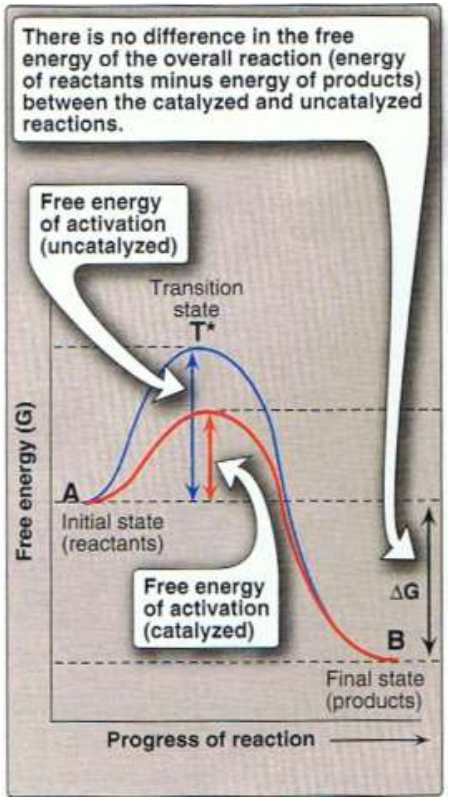
How enzymes work

- In each chemical reaction there is an energy barrier (energy of activation)

Ea

- For the molecules to react, they must overcome the energy barrier

- Enzymes reduce the energy of activation without affecting the free energy of the reactants and products and fasten the reaction rate



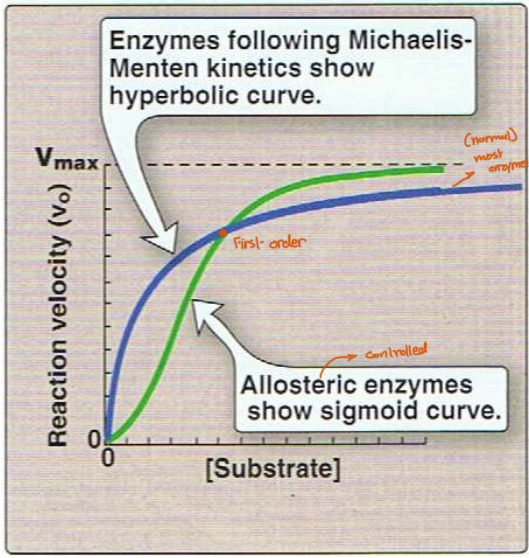
Factors affect Reaction velocity

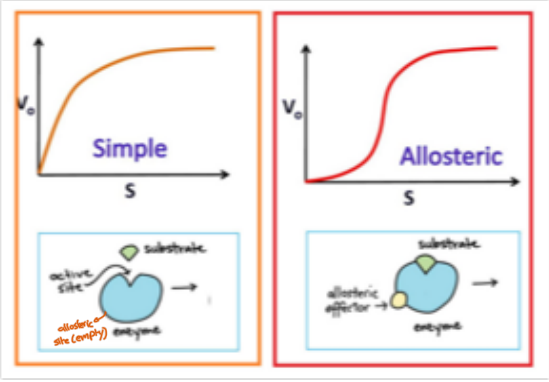
1 Substrate concentration ∝ V_{max}

- **Maximal velocity**: The rate of an enzyme-catalyzed reaction increases with substrate concentration until a maximal velocity (V_{max}) is reached (saturation with substrate of all available binding sites on the enzyme)

low conc of substrate → high affinity of enzymes (link faster)

- **Hyperbolic shape of the enzyme kinetics curve:** Most enzymes show Michaelis-Menten kinetics show hyperbolic curve while, allosteric enzymes frequently show a sigmoidal curve



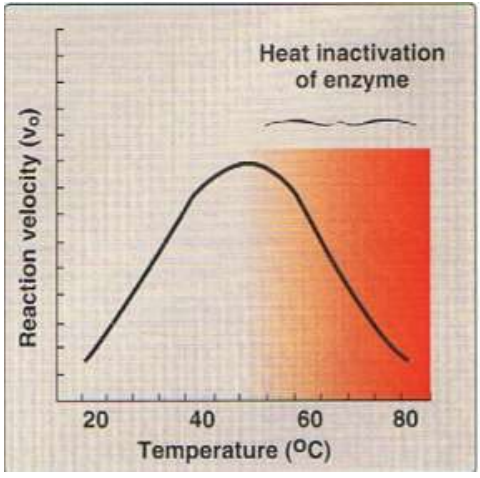


Reaction velocity

2 Temperature ∝ V

- Increase of velocity with temperature: The reaction velocity increases with temperature until a peak velocity is reached as a result of increased number of molecules having sufficient energy to pass over the energy barrier and form the products of the reaction.

- Decrease of velocity with higher temperature: as a result of temperature-induced denaturation of the enzyme



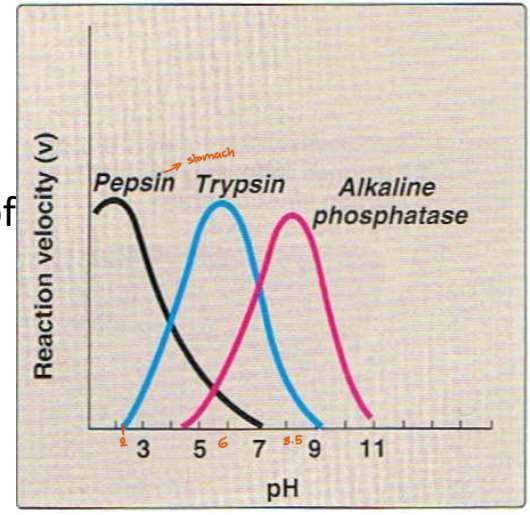
Reaction velocity

3 pH

- Effect of pH on the ionization of the active site: First, the catalytic process usually requires that the enzyme and substrate have specific chemical groups in either an ionized or unionized state in order to interact

- Effect of extremes of pH on enzyme denaturation: because the structure of the catalytically active protein molecule depends on the ionic character of the amino acid side chains.

- The pH optimum varies for different enzymes: often reflects the [H] at which the enzyme functions in the body



* Any enzyme present in the blood → optimum pH = 7.4 (physiological pH)

Inhibition of enzyme activity

- Inhibitor: any substance that can diminish the velocity of an enzyme-catalyzed reaction

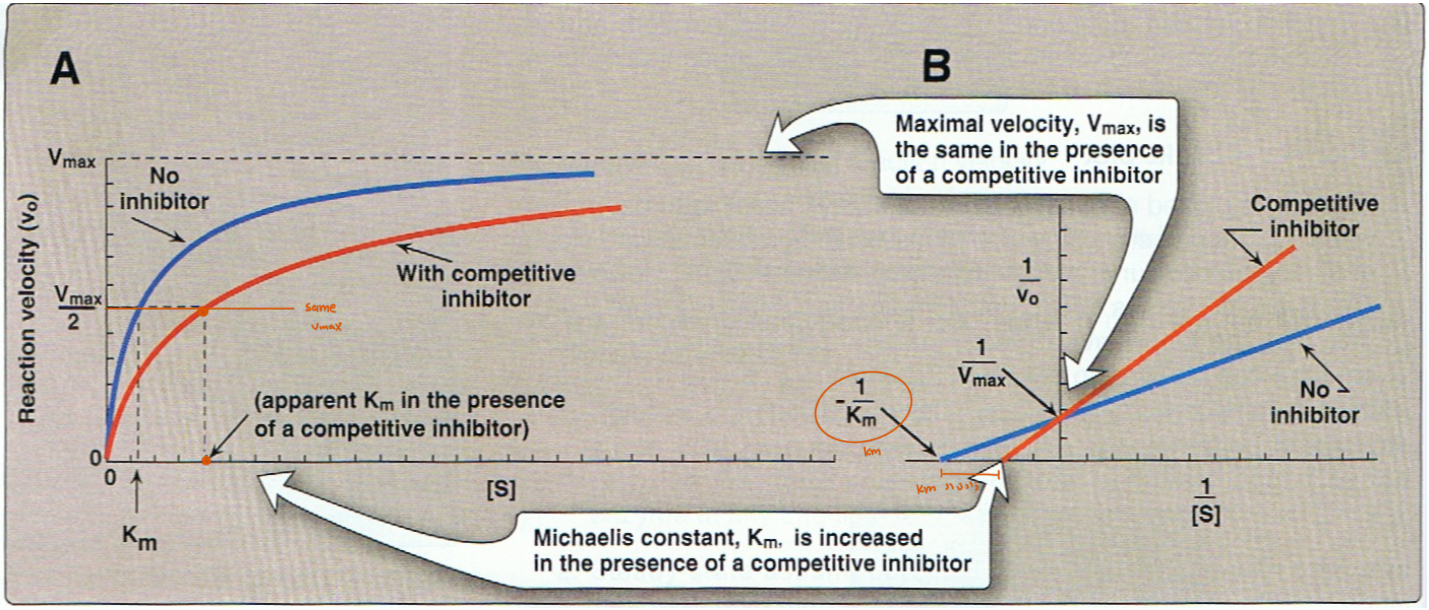
- Ⓐ **Reversible inhibitors**: bind to enzymes through noncovalent bonds. Dilution of the enzyme-inhibitor complex results in dissociation of the reversibly bound inhibitor, and recovery of enzyme activity

- Ⓑ **Irreversible inhibition**: occurs when an inhibited enzyme does not regain activity on dilution of the enzyme-inhibitor complex.

- The above types can be **competitive** or **noncompetitive**.

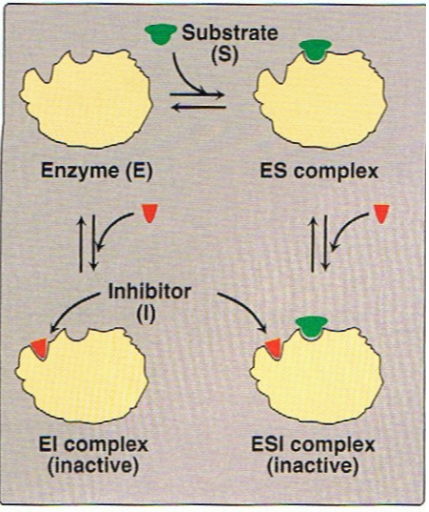
Inhibition of enzyme activity
① Competitive inhibitors

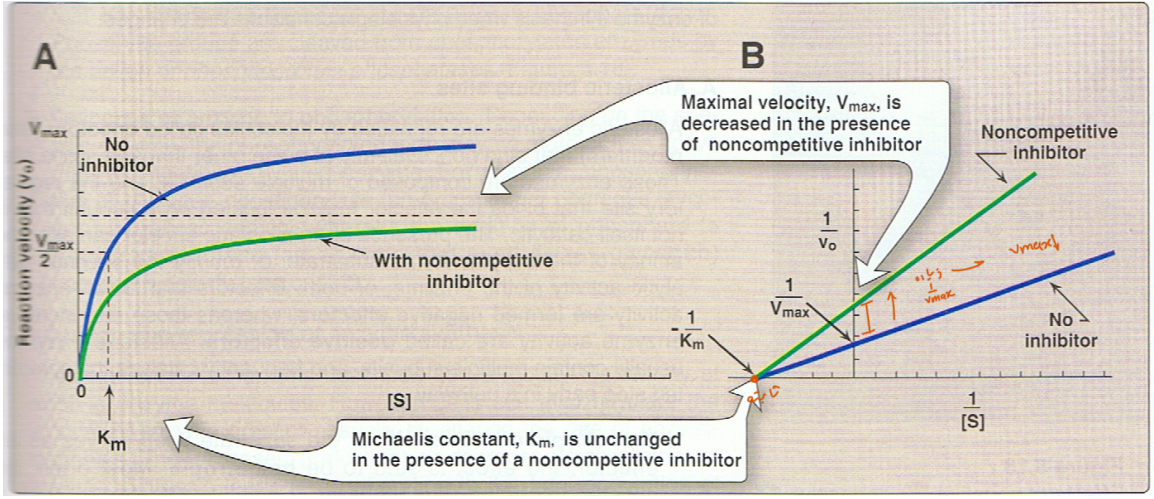
- occurs when the inhibitor competes with the substrate for the same site.
- Vmax is unchanged
- Apparant Km is increased
- statin drugs are example



Inhibition of enzyme activity
ⓘNoncompetitive inhibitors

- Occurs when the inhibitor and substrate bind at different sites on the enzyme.
- It can bind either free enzyme or the ES complex, thereby preventing the reaction from occurring
- Km is unchanged
- Vmax is decreased → changing the formation of enzyme (not normal → يكتاكد اني للتربع)





Examples on enzyme inhibitors

- non- competitive inhibitor: lead forms covalent bonds with the sulfhydryl side chains of cysteine in proteins

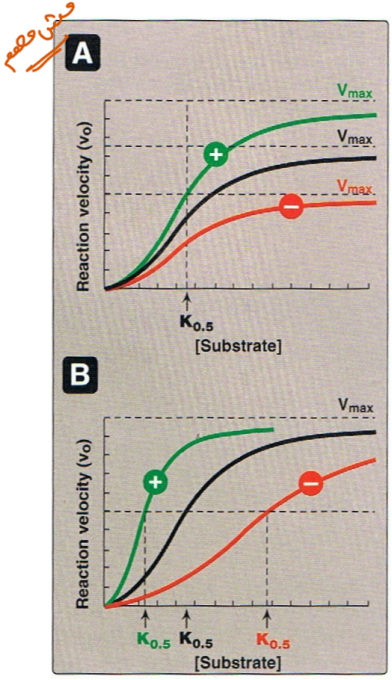
- Ferrochelatase, an enzyme that catalyzes the insertion of Fe+2 into protoporphyrin (a precursor of heme) is sensitive to inhibition by lead.

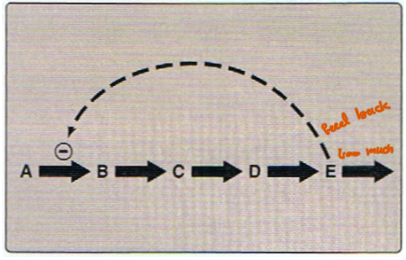
- as drugs
- The widely prescribed β-lactam antibiotics, such as penicillin and amoxicillin, act by inhibiting enzymes involved in bacterial cell wall synthesis
- Angiotensin-converting enzyme (ACE) inhibitors (captopril, enalapril, and lisinopril). They lower blood pressure by blocking the enzyme that cleaves angiotensin I to form the potent vasoconstrictor, angiotensin II

Regulation of enzyme activity (Allosteric regulation)

non-covalently

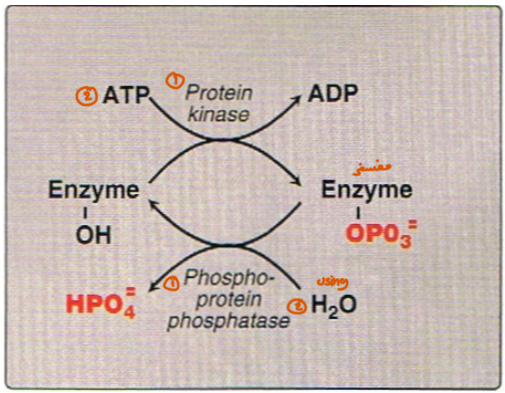
- Allosteric enzymes are regulated by compounds called effectors (or modifiers)
- Can have positive or a negative effect
- May affect the Vmax, Km or both.
- Can be (effectors / modifiers)
  1. homotropic (the substrate itself) sigmoidal shape curve
  2. heterotropic (the product or other subsance) feed back inhibition





Regulation of enzyme activity (Covalent modification)

- Phosphorylation (uses ATP as phosphate donor) or dephosphorylation by phosphoprotein phosphatases



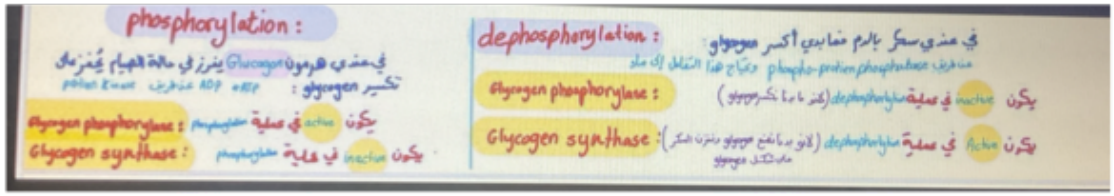
- The phosphorylated form of the enzyme can be more or less active

- مثال ١ Glycogen phosphorylase (glycogen degradation) increase activity upon phosphorylation
- مثال ٢ Glycogen synthase activity decreases

glycogen phosphorylase الفوسفرة تنشّط

glycogen synthase الفوسفرة تثبّط

induction and repression of enzyme synthesis due to the above factors



للتشخيص

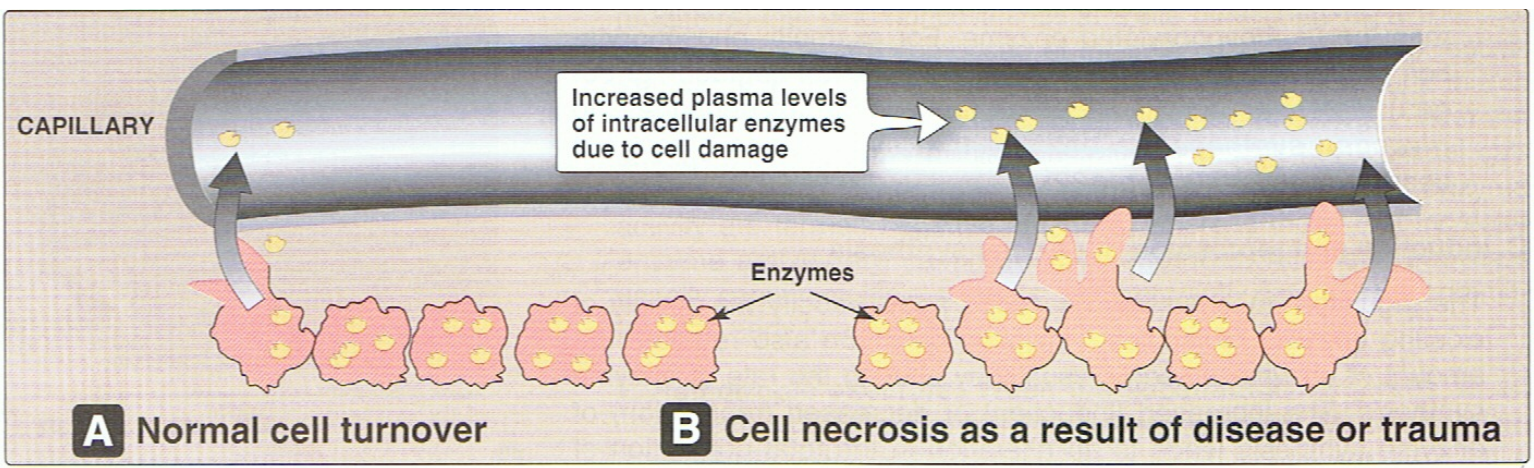
Enzymes in clinical diagnosis

Normal

➢ Low conc. of enzymes is present in blood due to cell turnover ← وجود

Upnormal

➢ Destruction of cells due to any damage may lead to release of some enzymes



Alteration of plasma enzyme levels in disease states

- The activities of many enzymes are routinely determined for diagnostic purposes in diseases of the heart, liver, skeletal muscle, and other tissues.

- The level of specific enzyme activity in the plasma frequently correlates with the extent of tissue damage.

- Determining the degree of elevation of a particular enzyme activity in the plasma is often useful in evaluating the prognosis for the patient.

Plasma enzymes as diagnostic tools

- Some enzymes show relatively high activity in only one or a few tissues.
- The presence of increased levels of these enzymes in plasma thus reflects damage to the corresponding tissue.
- For example, the enzyme alanine aminotransferase (**ALT**) is abundant in the liver. The appearance of elevated levels of ALT in plasma signals possible damage to **hepatic tissue**.
- This lack of tissue specificity limits the diagnostic value of many plasma enzymes.

more than one shape for the same enzyme

Isoenzymes and diseases of the heart

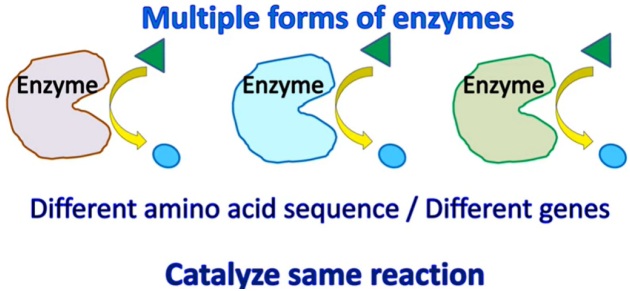
- Isoenzymes (or isozymes) are enzymes that catalyze the same reaction. However, they do not necessarily have the same physical properties because of genetically determined differences in amino acid sequence

- ✓ isoenzymes may be separated from each other by electrophoresis

- Different organs frequently contain characteristic proportions of different isoenzymes. The pattern of isoenzymes found in the plasma may, therefore, serve as a means of identifying the site of tissue damage.

- The plasma levels of creatine kinase (CK) and lactate dehydrogenase (LDH) are commonly determined in the diagnosis of myocardial infarction.

- They are particularly useful when the electrocardiogram is difficult to interpret, such as when there have been previous episodes of heart disease.



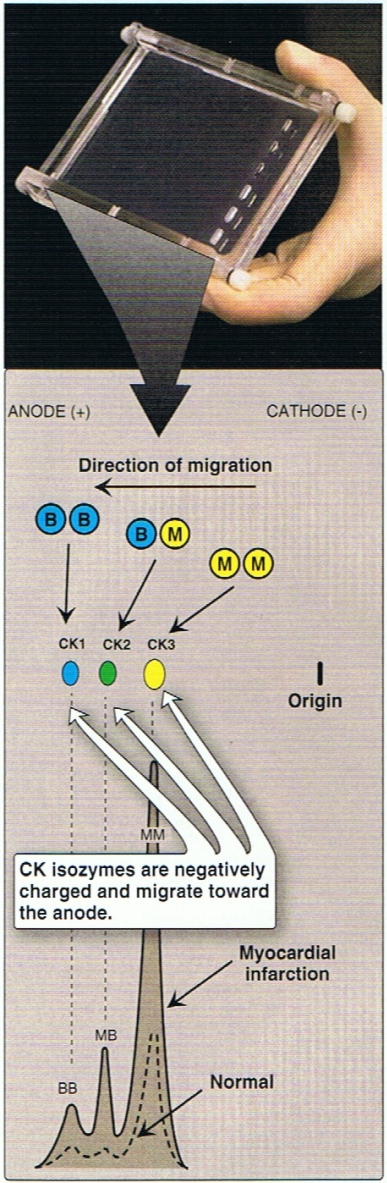
Quaternary structure of isoenzymes

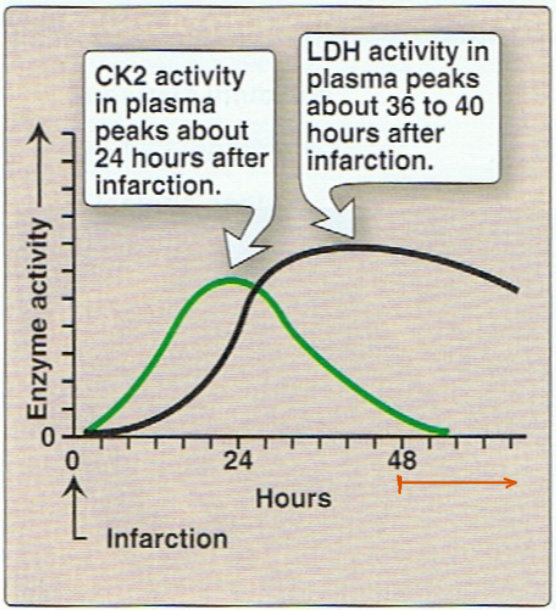
- Creatine kinase occurs as three isoenzymes. Each isoenzyme is a dimer composed of two polypeptides (called B and M subunits) associated in one of three combinations (CK1 = BB, CK2 = MB, and CK3 = MM). Each CK isoenzyme shows a characteristic electrophoretic mobility

- Myocardial muscle is the only tissue that contains more than five percent of the total CK activity as the CK2 (MB) isoenzyme.

- Appearance of this hybrid isoenzyme in plasma (four to eight hours following onset of chest pain which reaches peak after 24 hr) is virtually specific for infarction of the myocardium.

- Lactate dehydrogenase activity is also elevated in plasma following an infarction, peaking 36 to 40 hours after the onset of symptoms. LDH activity is, thus, of diagnostic value in patients admitted more than 48 hours after the infarction


ANODE (+)
CATHODE (-)
Direction of migration
B B
B M
M M
CK1
CK2
CK3
Origin
MM
CK isozymes are negatively charged and migrate toward the anode.
Myocardial infarction
MB
BB
Normal


CK2 activity in plasma peaks about 24 hours after infarction.
LDH activity in plasma peaks about 36 to 40 hours after infarction.
Enzyme activity
0
0
24
48
Hours
Infarction

Newer markers for myocardial infarction

- Troponin T and troponin I are regulatory proteins involved in myocardial contractility.
- They are released into the plasma in response to cardiac damage.
- Elevated serum troponins are more predictive of adverse outcomes in unstable angina or myocardial infarction than the conventional assay of CK2

Notes	Diagnostic Value	Time to Peak	Time of Appearance in Plasma	Marker
Described as a hybrid isoenzyme	Virtually specific for infarction of the myocardium	Peaks at 24 hours	4–8 hours after onset of chest pain	**Hybrid isoenzyme (CK-MB)**
Activity is elevated in plasma following an infarction	Valuable in patients admitted more than 48 hours after infarction	Peaks at 36–40 hours after symptoms	Not specified	**Lactate Dehydrogenase (LDH)**
Regulatory proteins involved in myocardial contractility	More predictive of adverse outcomes in unstable angina or myocardial infarction than the conventional assay of CK2	Not specified	Released into plasma in response to cardiac damage	**Troponin T and Troponin I**

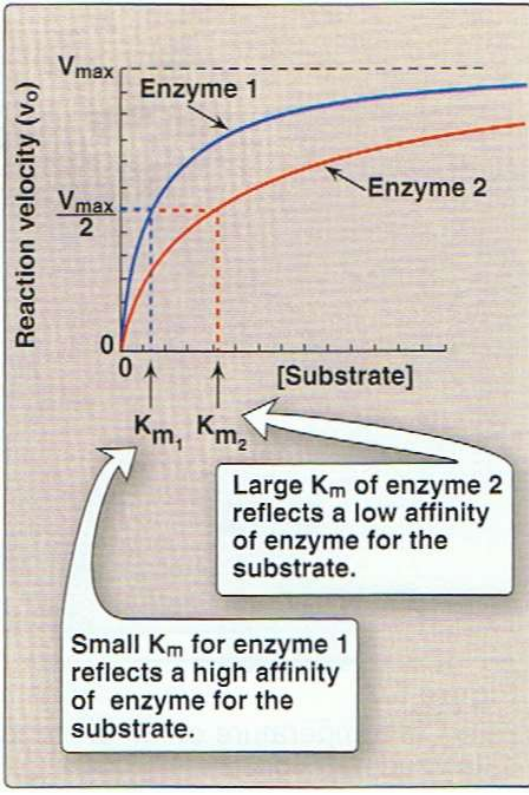
Calculation :

Michaelis-Menten equation

$$v_o = \frac{V_{max}[S]}{K_m + [S]}$$

[S] at max $\frac{V}{2}$

- Where
  - v_o = initial reaction velocity
  - V_{max} = maximal velocity
  - K_m = Michaelis constant ~~= (k-1 +k2)/k1~~
  - [S] = substrate concentration
- Velocity of the reaction is directly proportional to the enzyme concentration



افترضنا

- assumptions made in deriving the Michaelis-Menten rate:

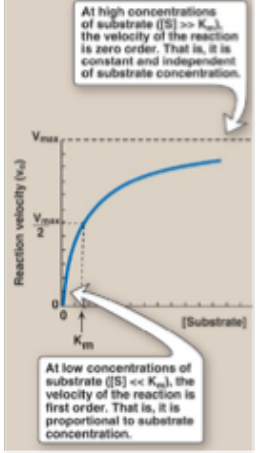
1. The conc. of substrate [S] is much greater than the conc. of enzyme [E]
2. [ES] does not change with time (the steady-state assumption

Michaelis-Menten constant

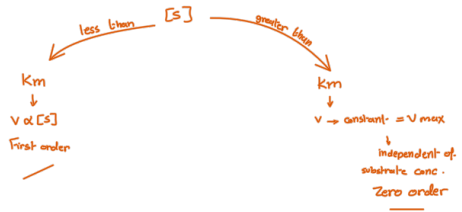
* تركيز متفاعل معين حتى يعطيني اعلى
$V = \frac{V_{max}}{2}$ التركيز عندما ← affinity

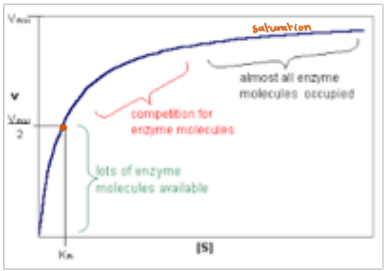
- K_m-the Michaelis constant- is characteristic of an enzyme and its particular substrate, and reflects the affinity of the enzyme for that substrate
- K_m is numerically equal to the substrate concentration at which the reaction velocity is equal to 1/2 V_{max}
- K_m does not vary with the concentration of enzyme
- Small K_m reflects a high affinity of the enzyme for substrate, because a low concentration of substrate is needed to half-saturate the enzyme
- Large K_m reflects a low affinity of enzyme for substrate because a high concentration of substrate is needed

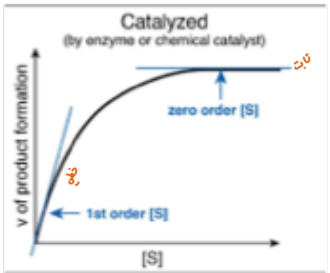
Michaelis-Menten constant



- The rate of the reaction is directly proportional to the enzyme concentration at all substrate concentrations [S] ∝ V_{max}
- For example, if the enzyme concentration is halved, the initial rate of the reaction (v_o), as well as that of V_{max}, are reduced to one half that of the original. $\frac{[S]}{2} \rightarrow \frac{v_o}{2} \rightarrow \frac{V_{max}}{2}$
- When [S] is much less than K_m, the velocity of the reaction is approximately proportional to the substrate concentration (first order)
- When [S] is much greater than Km, the velocity is constant and equal to V_{max}. The rate of reaction is then independent of substrate concentration (zero order)





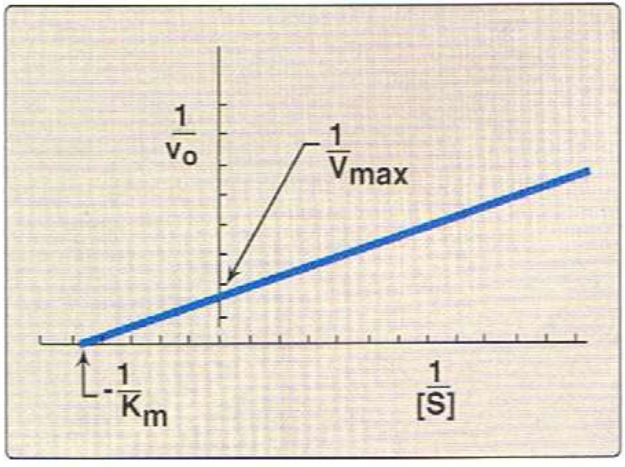


Linearization of Michaelis-Menten equation (Lineweaver-Burke plot)

- It is not always possible to determine the V_{max} from plotting v_o against [S]

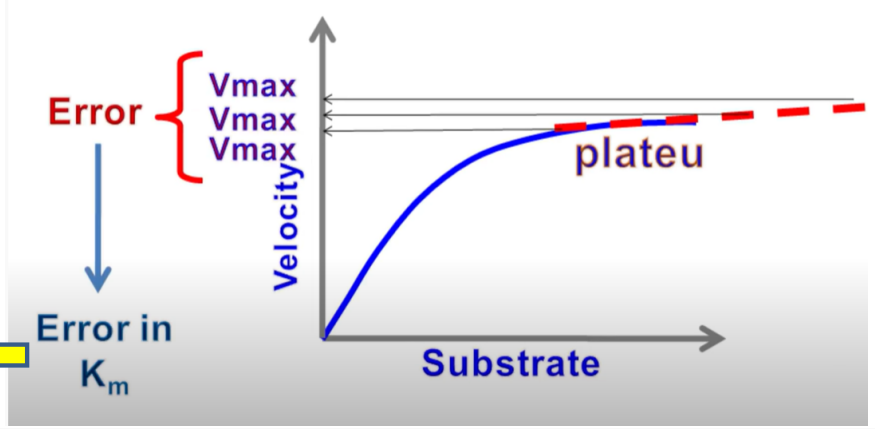
$$\frac{1}{v_o} = \frac{K_m}{V_{max}[S]} + \frac{1}{V_{max}}$$

- The intercept on the x axis = $-1/K_m$
- The intercept on the y axis = $1/V_{max}$



* $K_m = [S] \rightarrow$ when $V = \frac{1}{2} V_{max}$

Why do we do a Linearization of Michaelis-Menten equation- (Lineweaver-Burke plot)



Will not give accurate value of Km

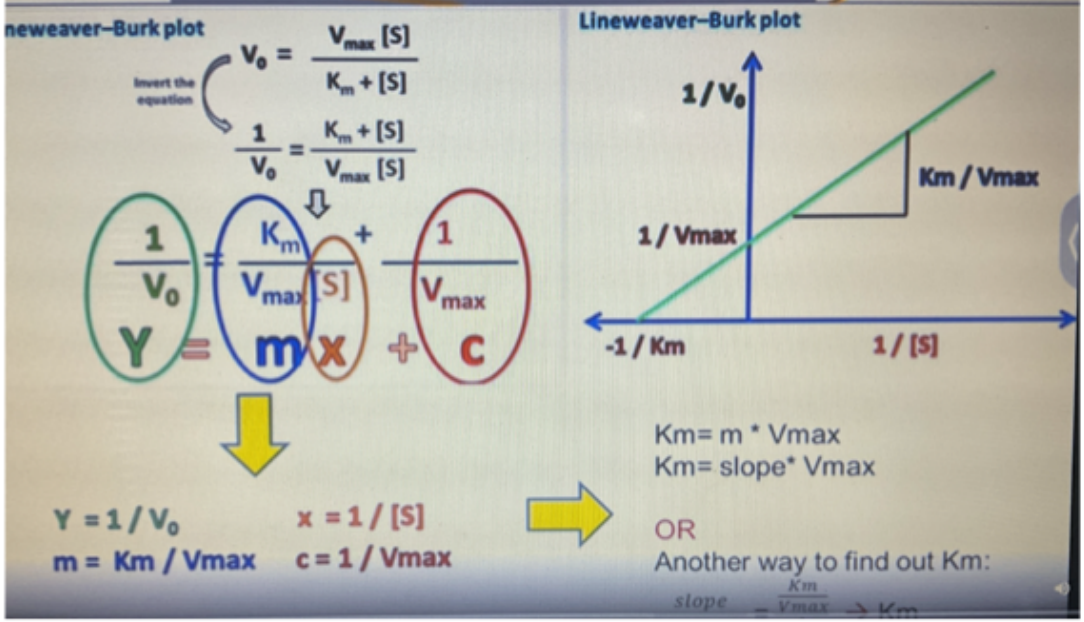
Lineweaver–Burk plot

Invert the equation

$$V_0 = \frac{V_{max}[S]}{K_m + [S]}$$

$$\frac{1}{V_0} = \frac{K_m + [S]}{V_{max}[S]}$$

$$\frac{1}{V_0} = \frac{K_m}{V_{max}[S]} + \frac{[S]}{V_{max}[S]}$$



$Y = mx + c$ — معادلة خط مستقيم

$\frac{1}{V_0} = 0.02\,[\frac{1}{S}] + 0.05$ → سؤال

$\frac{1}{V_0} = \frac{Km}{Vmax}[\frac{1}{S}] + \frac{1}{Vmax}$

$\therefore Vmax = \frac{1}{0.05} = \frac{1}{\frac{5}{100}} = 1 * \frac{100}{5} = 20$

$0.02 = m = \frac{Km}{Vmax}$ → $\therefore Km = Vmax\,(0.02)$

$Km = 20\,(0.02) = 0.04$

∴ to find Km :

① $Km = m * Vmax$

② $Km = \frac{slope}{intercept} = \frac{\frac{Km}{Vmax}}{\frac{1}{Vmax}}$

③ $Km = \frac{intercept\ with\ x\ axess}{(-\frac{1}{Km})}$

Km= m * Vmax
Km= slope* Vmax

OR

Another way to find out Km:

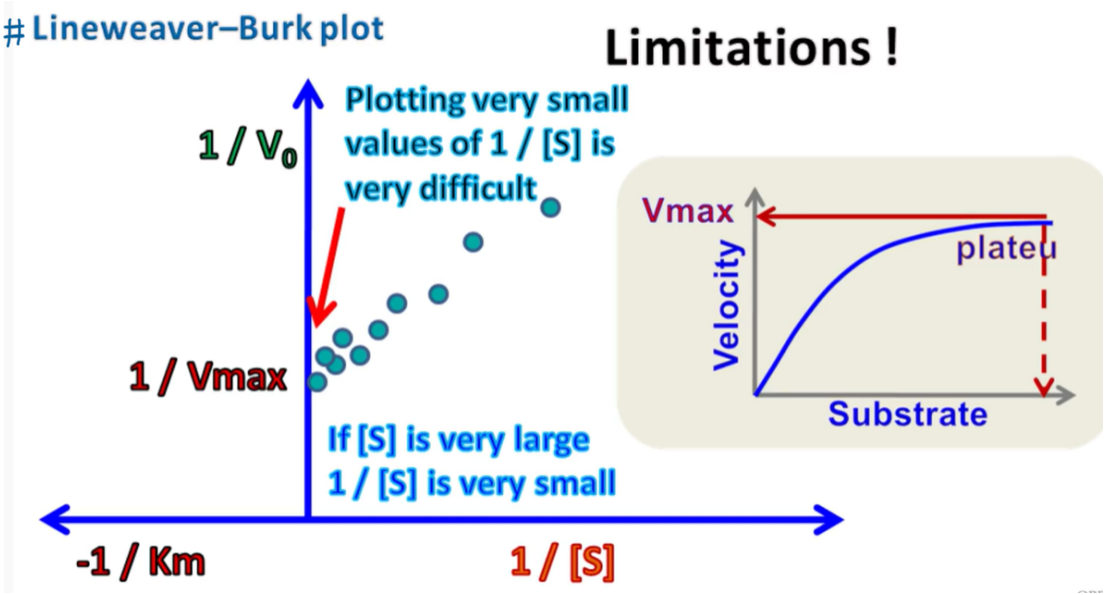
$\frac{slope}{intercept} = \frac{\frac{Km}{Vmax}}{\frac{1}{Vmax}}$ → Km

↳ $-\frac{1}{Km}$ or $\frac{1}{Vmax}$

OR

By extrapolating the line to the X-intercept.

- Velocity (V_o) unit is concentration/time (i.e. mmole/L/min)
- Km unit is concentration (same as substrate unit given in the question)



Limitiation:

- 1. You have to be careful to the interpretation of the inverse values: $\frac{1}{V_\circ}$ and $\frac{1}{[s]}$.
- Plotting very small values of $\frac{1}{[s]}$ can be challenging, however,

Enzyme questions

1. The kinetics of an enzyme are measured as a function of substrate concentration in the presence and absence of 100 mM inhibitor.

b) What are the values of *V*max and *K*M in the presence of this inhibitor?

c) What type of inhibition is it?

[S] (mM)	Velocity (mmol/L/minute)	
	No inhibitor	Inhibitor
3	10.4	2.1
5	14.5	2.9
10	22.5	4.5
30	33.8	6.8
90	40.5	8.1

AutoSave Off enzyme-1

Search (Alt+Q)

File Home Insert Page Layout Form Pivot

PivotTable Recommended PivotTables Table Illustrations Tables

Chart 3D Map Tours Line Column Win/ Loss Sparklines

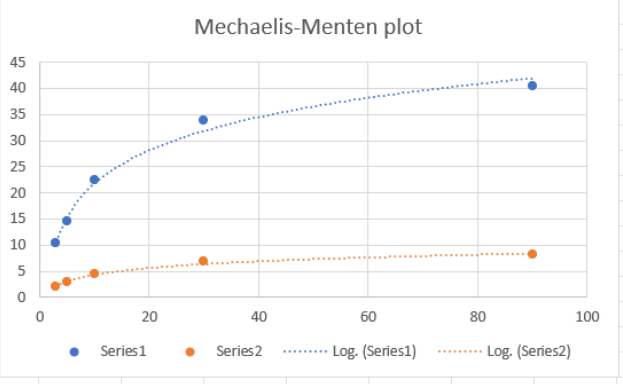
Let us have a try on excel

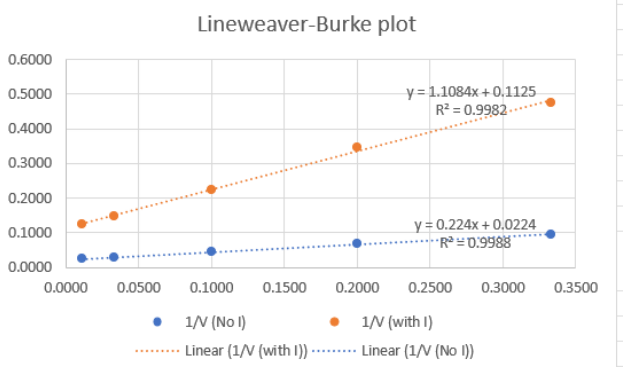
Q5

		Velocity (mM/min)	
	Substrate-(mM)	No inhibitor	with inhibitor
	3	10.4	2.1
	5	14.5	2.9
	10	22.5	4.5
	30	33.8	6.8
	90	40.5	8.1

		Velocity (mM/min)	
	Substrate-(mM)	No inhibitor	with inhibitor
	1/s	1/V (No I)	1/V (with I)
	0.3333	0.0962	0.4762
	0.2000	0.0690	0.3448
	0.1000	0.0444	0.2222
	0.0333	0.0296	0.1471
	0.0111	0.0247	0.1235

		No inhibitor	with inhibitor
	Slope	0.2240	1.1080
	Intercept	0.0220	0.1120
	Vmax=1/intercept	45.4545	8.9286
	Km=(slope*Vmax) or Km=(slope/intercept)	10.1818	9.8929





Enzyme questions-answers

1. The kinetics of an enzyme are measured as a function of substrate concentration in the presence and absence of 100 mM inhibitor.

b) What are the values of *V*max and *K*M in the presence of this inhibitor?

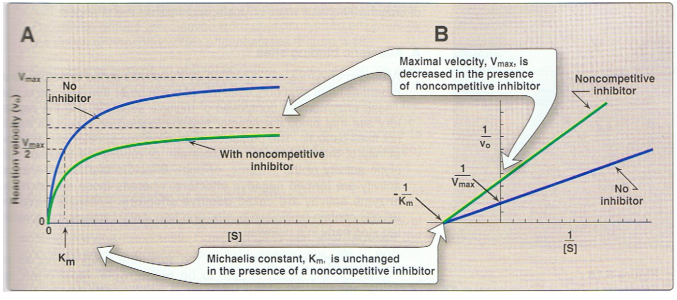
Without inhibitor Vmax= 45.45 mmole/L/minute, Km= 10.18 mM

With inhibitior Vmax= 8.92 mmole/L/minute, Km= 9.8929 mM

c) What type of inhibition is it?

Noncompetitive inhibitor (km did not change), Vmax also decreased

Remember !



$$\frac{1}{V_o} = \frac{Km}{V_{max}} \cdot \frac{1}{[S]} + \frac{1}{V_{max}}$$

same as subs unit بالوحدات

V_o ← mmol/L/min

الآلة الحاسبة :-

Mode → 3 (REG) → 1 (lin) → M+ (جذر) → AC

* To solve the EQ :- Shift → 2

A ← intercept

B ← slope

r → correction coefficient

$$y = BX + A$$

$$\frac{Km}{V_{max}} = B \quad / \quad \frac{1}{V_{max}} = A$$

How to judge if Km values are equal?

Subtract the value of Km and divide the answer by any km value*100

So

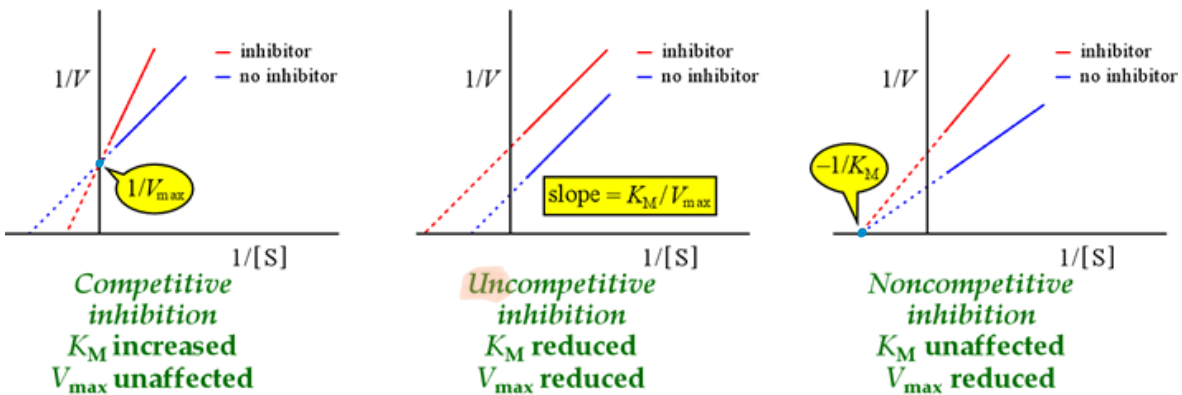
10.18-9.892=0.288

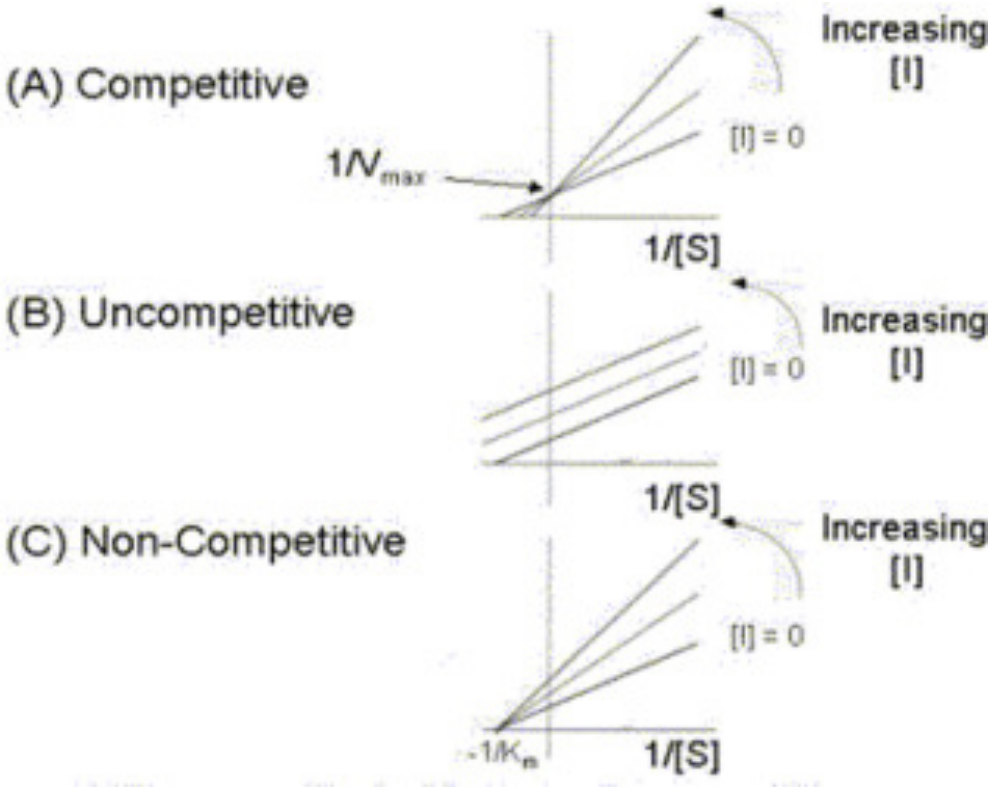
0.288/10.18*100=2.8% (Km is considered as unchanged if you obtain any difference value below than 10%□ probably due to experimental error).

Summary

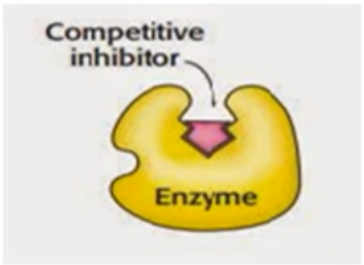
Type of inhibitor	Vmax	Km
competitive inhibitor	unchanged	increased ✓
non-competitive inhibitor	decreased ✓	unchanged ✓
uncompetitive inhibitor	decreased	decreased

The Lineweaver-Burk plots for inhibition



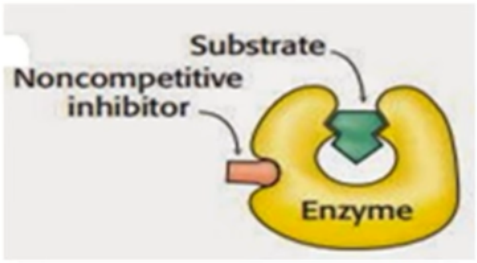

(A) Competitive
Increasing
[I]
[I] = 0
1/V_max
1/[S]
(B) Uncompetitive
Increasing
[I]
[I] = 0
1/[S]
(C) Non-Competitive
Increasing
[I]
[I] = 0
-1/K_m
1/[S]

Competitive Inhibition



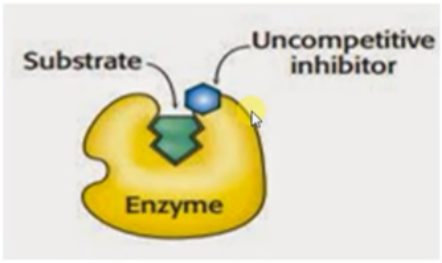
Inhibitor→Active site

Non-competitive inhibition

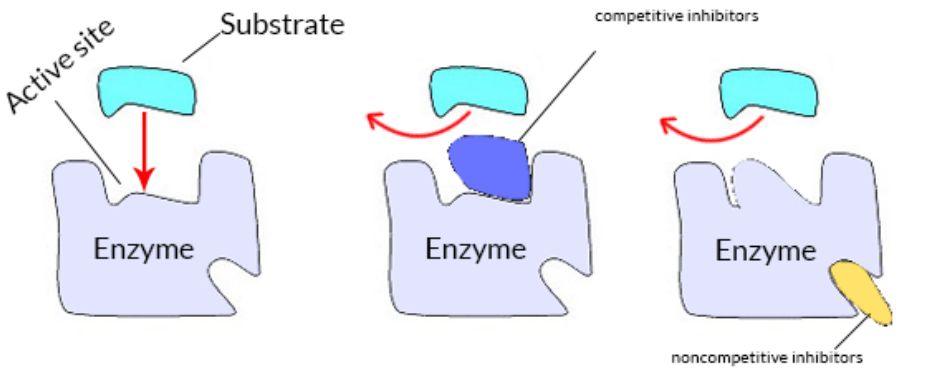


Inhibitor→Allosteric site

Uncompetitive inhibition



Inhibitor→ES complex



(a) Substrate can normally bind to active site of enzyme.

(b) Competitive inhibitor mimics substrate and competes for active site.

(c) Noncompetitive inhibitor alters conformation of enzyme so active site is no longer fully functional.

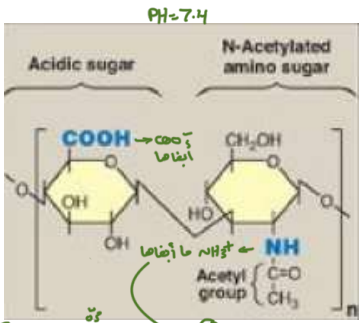
Glycosaminoglycans

suger proline polysacarride

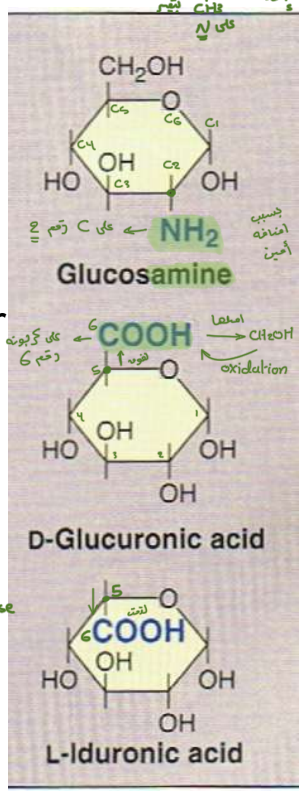
* structures that support a specific region

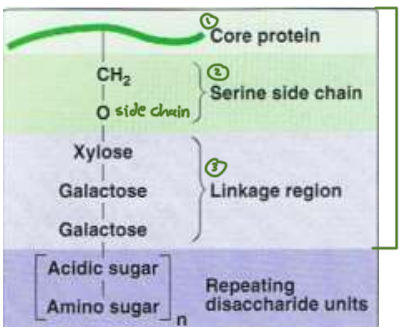
other name → **mucopolysaccharides**

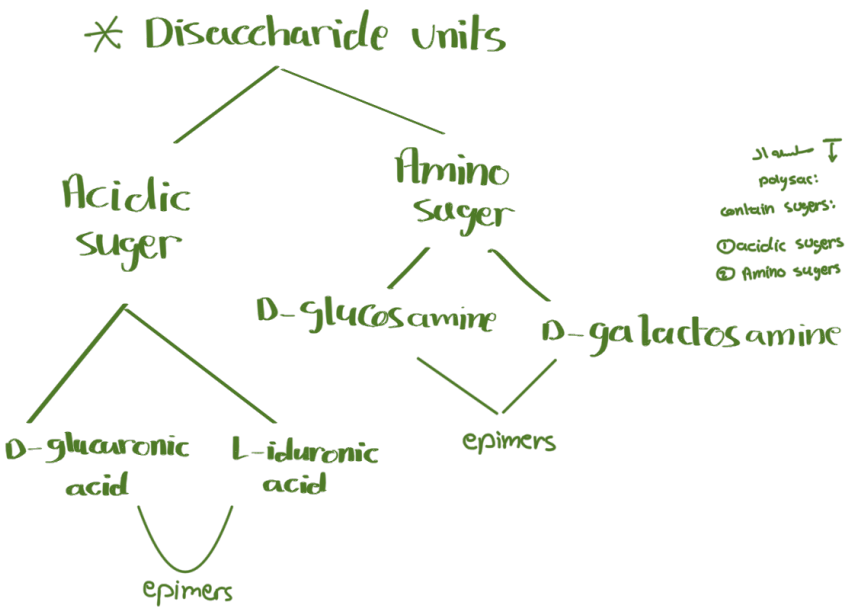
Glycosaminoglycans



- Are long, negatively charged, unbranched, heteropolysaccharide chains generally composed of a repeating disaccharide unit [acidic sugar-amino sugar]n
- The amino sugar is either D-glucosamine or D-galactosamine in which the amino group is usually acetylated, thus eliminating its positive charge
- The amino sugar may also be sulfated on carbon 4 or 6 or on a nonacetylated nitrogen.
- The acidic sugar is either D-glucuronic acid or its carbon-5 epimer, L-iduronic acid.







Glycosaminoglycans (GAG)

- These compounds bind large amounts of water, thereby producing the gel-like matrix that forms the basis of the body's ground substance.
- The viscous, lubricating properties of mucous secretions are also caused by the presence of glycosaminoglycans, which led to the original naming of these compounds as **mucopolysaccharides**.
- As essential components of cell surfaces, GAGs play an important role in **mediating cell-cell signaling** and **adhesion**

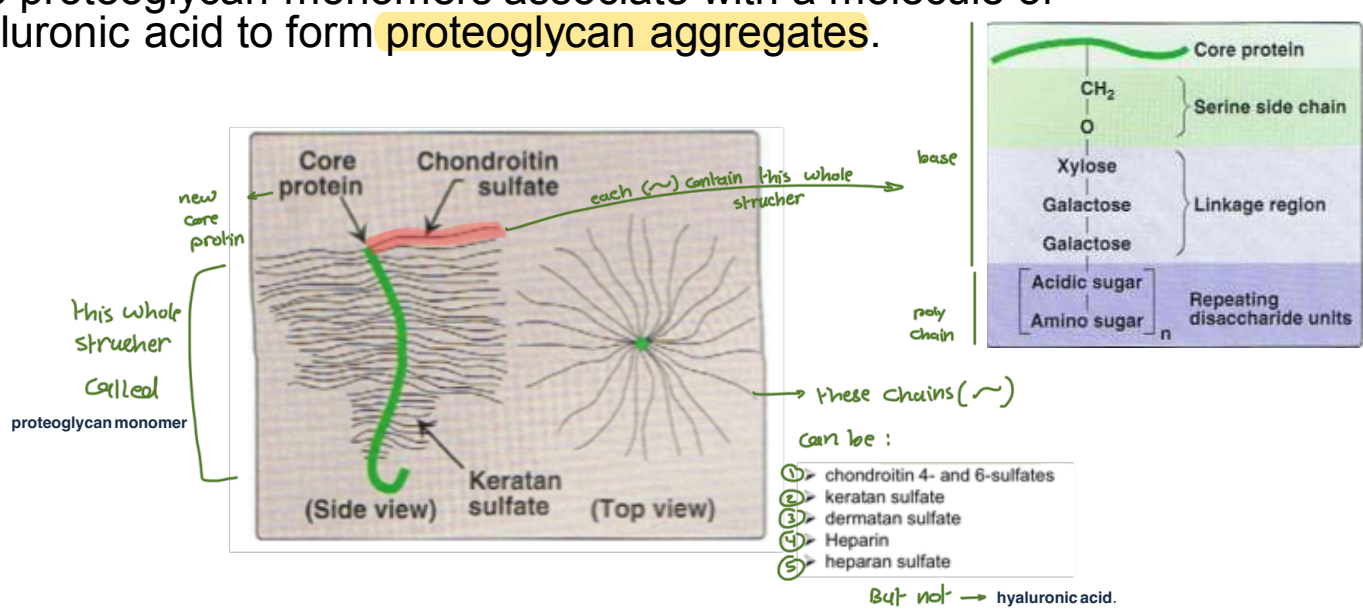
Classes of GAGs

- There are six major classes of glycosaminoglycans, including:
  - chondroitin 4- and 6-sulfates
  - keratan sulfate
  - dermatan sulfate
  - Heparin
  - heparan sulfate
  - hyaluronic acid.

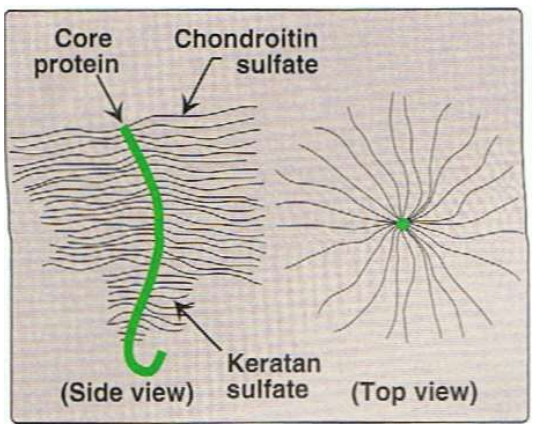
can't attached it to the core protin

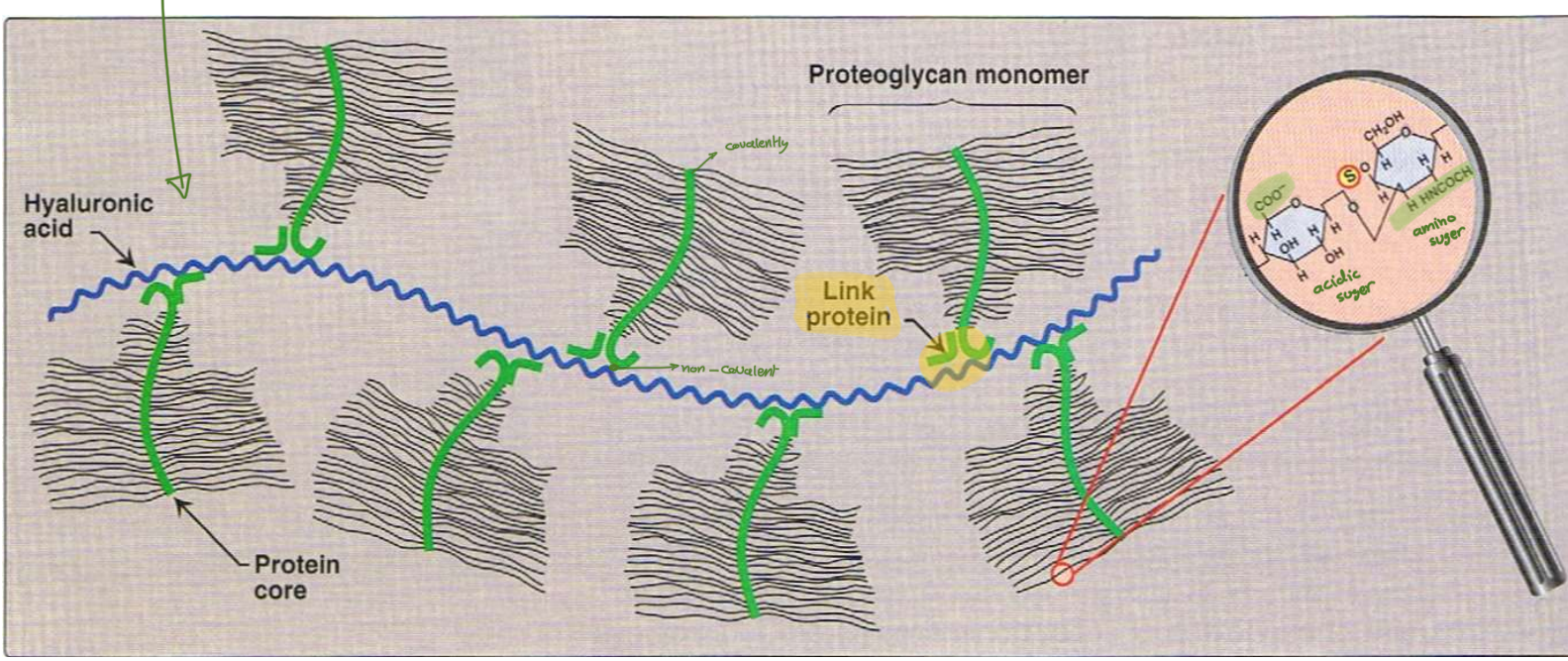
- All of the GAGs, except hyaluronic acid, are found covalently attached to protein, forming proteoglycan monomers, which consist of a core protein to which the linear GAG chains are covalently attached

- The proteoglycan monomers associate with a molecule of hyaluronic acid to form proteoglycan aggregates.



طيب شو بعمل باد Hyaluronic acid لعاد ؟





proteoglycan monomers + hyaluronic acid = **proteoglycan aggregate**

imp

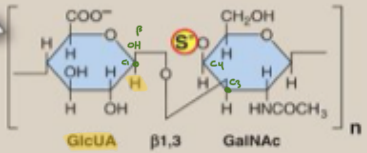
GlcUA: glucouronic acid
GalNAc: N-acetyl galactosamine
GlcNAc: N-acetyl glucosamine
Gal: galactose
GlcN: glucosamine

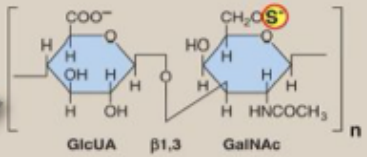
① CHONDROITIN 4- AND 6-SULFATES

repeating disaccharide unit

- Disaccharide unit:
  - a N-acetylgalactosamine with (S) on either carbon (C) 4 or C 6 and glucuronic acid b
- Most abundant GAG in the body
- Found in cartilage, tendons, ligaments, and aorta
- Form proteoglycan aggregates, through noncovalent association with hyaluronic acid
- In cartilage, bind collagen and hold fibers in a tight, strong network

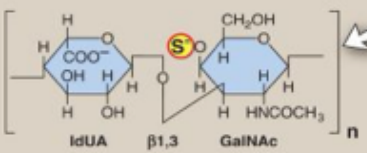
وظيفته بال cartilage





② DERMATAN SULFATE

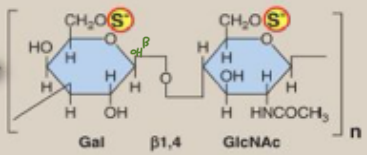
- Disaccharide unit:
  - a N-acetylgalactosamine and
  - b L-iduronic acid (with variable amounts of glucuronic acid)
- Found in skin, blood vessels, and heart valves



③ KERATAN SULFATES (KS) I and II

Aminosugar + sugar عادي حمض Acidic

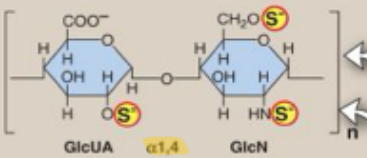
- Disaccharide unit:
  - a N-acetylglucosamine and
  - b galactose (no uronic acid); (S) may be present on C 6 of either sugar
- Most heterogeneous GAG because they contain additional monosaccharides such as L-fucose, N-acetyl-neuraminic acid, and mannose
- KS I found in corneas; KS II found in loose connective tissue proteoglycan aggregates with chondroitin sulfate



④ HEPARIN

- Disaccharide unit:
  - a Glucosamine and glucuronic or iduronic acid; most glucosamine residues are bound in sulfamide linkages; sulfate also found on C 3 or C 6 of glucosamine and C 2 of uronic acid (an average of 2.5 (S) per disaccharide unit)
- α-Linkage joins the sugars
- Unlike other GAG that are extracellular compounds, heparin is an intracellular component of mast cells that line arteries, especially in liver, lungs, and skin
- Serves as an anticoagulant

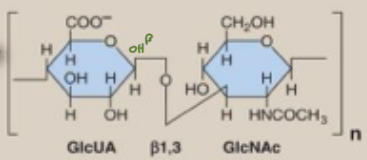
sulfation of NH2 to H-N-S



⑤ HYALURONIC ACID

- Disaccharide unit:
  - a N-acetylglucosamine and
  - b glucuronic acid
- Different from other GAG: not sulfated, not covalently attached to protein, and not limited to animal tissue but also found in bacteria
- Serves as a lubricant and shock absorber
- Found in synovial fluid of joints, vitreous humor of the eye, the umbilical cord, loose connective tissue, and cartilage

no negative charge sours of S just coo⁻



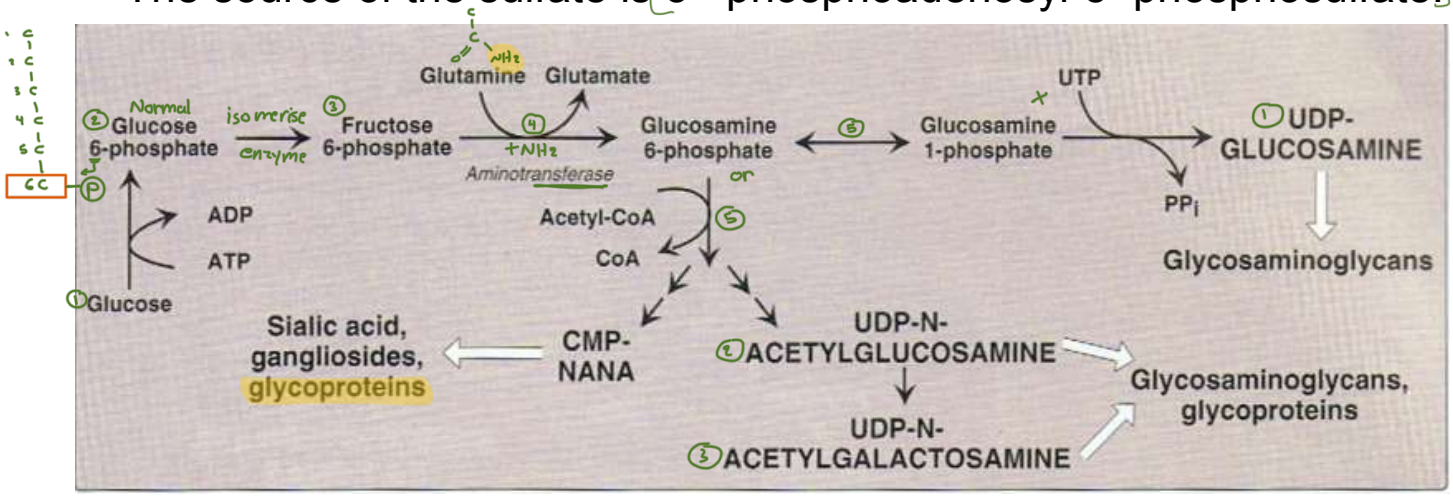
HEPARAN SULFATE

- Disaccharide unit:
  - Same as heparin except some glucosamines are acetylated, and there are fewer (S)
- Extracellular GAG found in basement membrane and as a ubiquitous component of cell surfaces

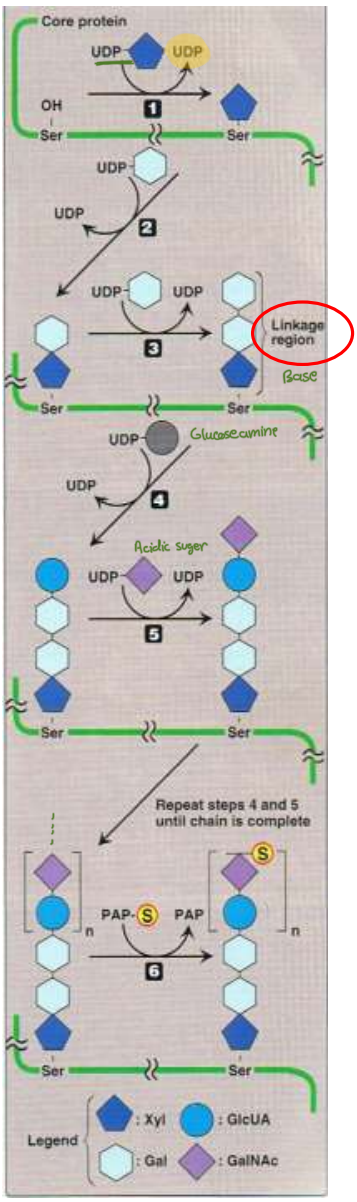
GAG Class	Disachride units	S location (C No.)	locations	Notes
chondroitin	① N-acetylgalactosamine ② glucuronic acid	S on: 4 or 6	① cartilage ② tendons ③ ligaments ④ aorta	– most abundant in body – bind collagen and hold fibers in a tight, strong network → in cartilage
keratan I II	① N-acetylglucosamine ② galactose (no uronic acid)	S on C_6 on either one of these two sugars	I: Corneas II: loose connective	– most heterogeneous – Contain additional monosachanid ① L-fucose ② N-acetyl neuraminic ③ mannose
dermatan	① N-acetylgalactosamine ② L-iduronic acid (with amounts of glucuronic acid)	—	skin / blood vessels / heart values	—
Heparin	① Glucosamine (sulfated) ② glucuronic / iduronic	S on: C_3 or C_6 S on: C_2	lung / liver / skin	– only α – intracellular component of mast cells that line arteries – Anticoagulant
heparan	① Glucosamine (sulfated/acetylated) ② 〃	〃	– basement membrane – cell surfaces	– less sulfate than heparin —
hyaluronic	① N-acetylglucosamine ② glucuronic acid	—	– synovial fluid of joints – vitreous humor of eye – umbilical cord – loose conn – cartilage	– not sulfated – not covalently attached to protein – not limited in animals: found in bacteria – serves as lubricant / shock absorber

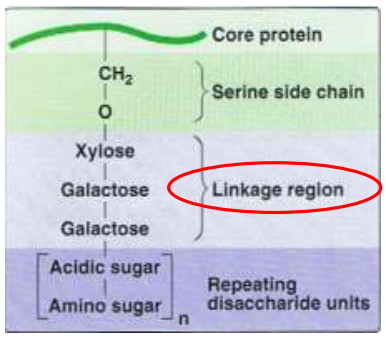
Synthesis of Glycosaminoglycans

- GAGs are synthesized in the endoplasmic reticulum and the Golgi
- The polysaccharide chains are elongated by the sequential addition of alternating acidic and amino sugars, donated by their UDP-derivatives
- The last step in synthesis is sulfation of some of the amino sugars. The source of the sulfate is 3'- phosphoadenosyl-5'-phosphosulfate.



PAP-S : 3’- phosphoadenosyl-5’-phosphosulfate





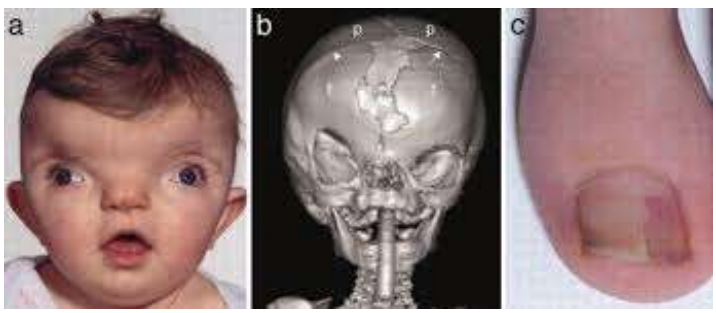
Mucopolysaccharidosis

Disorder : I can't- breakdown GAGs

- Glycosaminoglycans are degraded by lysosomal hydrolases (inside the cell). They are first broken down to oligosaccharides, which are degraded sequentially from the non-reducing end of each chain

GAG
↓ breaks to
oligosaccharides
↓ breaks
from the middle (non-reducing end)

- A deficiency of one of the hydrolases results in a mucopoly-saccharidosis.
- These are hereditary (وراثي) disorders in which glycosaminoglycans accumulate in tissues, causing symptoms (تشوهات) such as skeletal and extracellular matrix deformities, and mental retardation (عقلي)
- Examples (تخلف) of these genetic diseases include Hunter ① and Hurler ② syndromes



Glycoproteins

sugers + proteins

- Glycoproteins are proteins to which oligosaccharides are covalently attached. → to the proteins

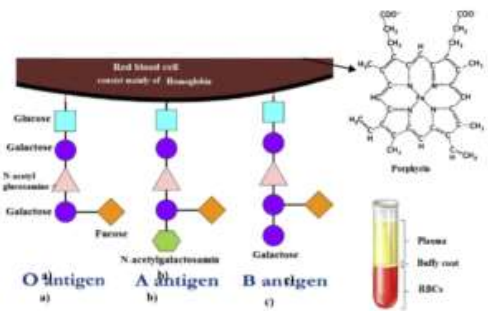
  type of suger : (2-10) units

- They differ from the proteoglycans in that the length of the glycoprotein's **carbohydrate chain is relatively short** (usually two to ten sugar residues long, although they can be longer)

- The carbohydrates of glycoproteins **do not have serial repeats** as do glycosaminoglycans.

Function of glycoproteins

- Membrane-bound glycoproteins participate in a broad range of cellular phenomena, including:
  - Cell surface recognition (by other cells, hormones, viruses)
  - Cell surface antigenicity (such as the blood group antigens)
  - As components of the extracellular matrix and of the mucins of the gastrointestinal and urogenital tracts, where they act as protective biologic lubricants.
    * Main components of of mucus that lines the GIT, UT → mucins
  - Almost all of the globular proteins present in human plasma are glycoproteins.



Synthesis of Glycoproteins

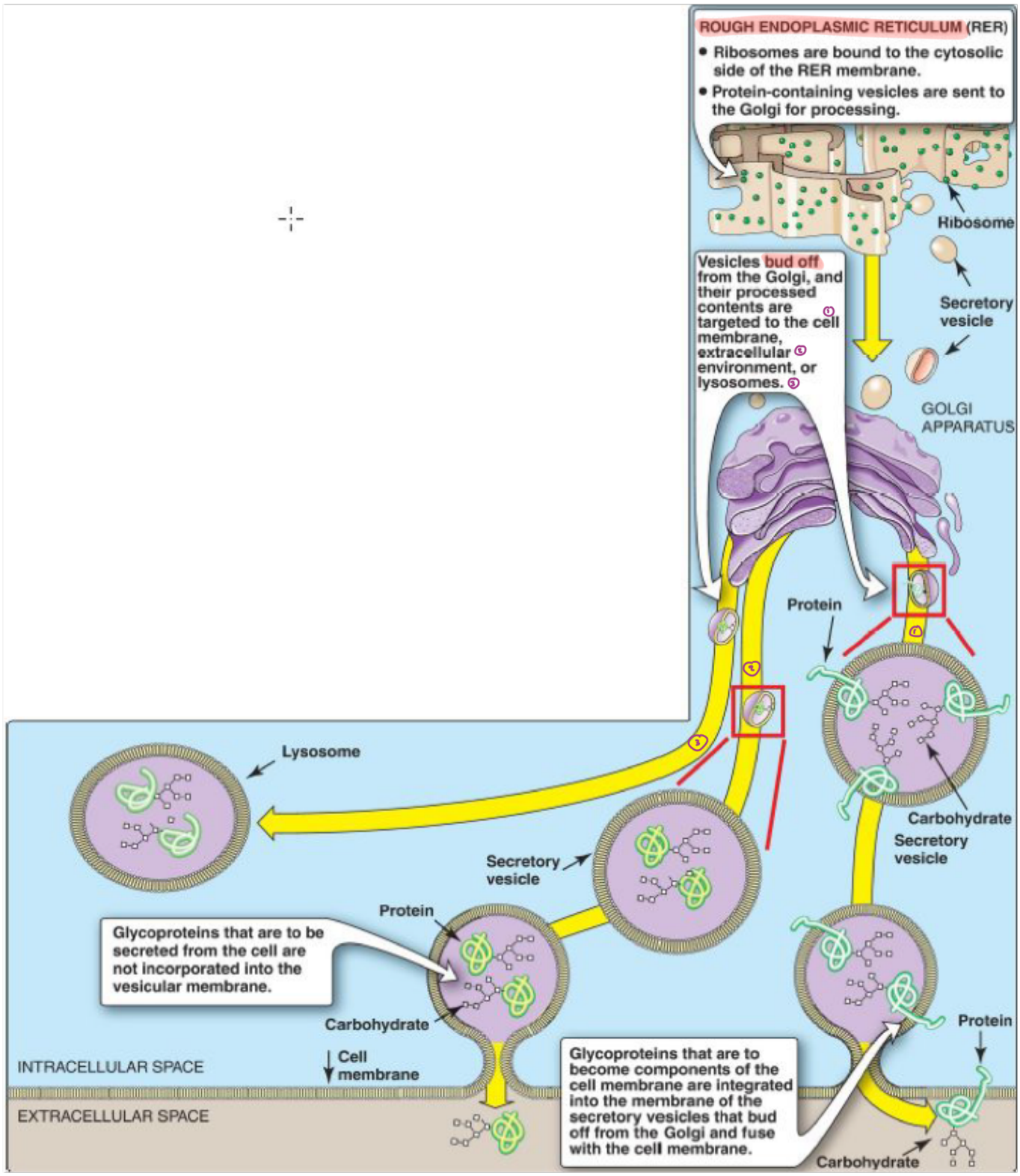
- Glycoproteins are synthesized in the endoplasmic reticulum and the Golgi.
- The precursors of the carbohydrate components of glycoproteins are sugar nucleotides.
- O-linked glycoproteins are synthesized by the sequential transfer of sugars from their nucleotide carriers to the protein
- N-linked glycoproteins contain varying amounts of mannose. They are synthesized by the transfer of a pre-formed oligosaccharide from its membrane lipid carrier, **dolichol**, to the protein
- They also require **dolichol**, an intermediate carrier of the growing oligosaccharide chain.

"المركّبات التي تسبق تكوين مكونات الكربوهيدرات في البروتينات السكرية هي نوكليوتيدات السكر."

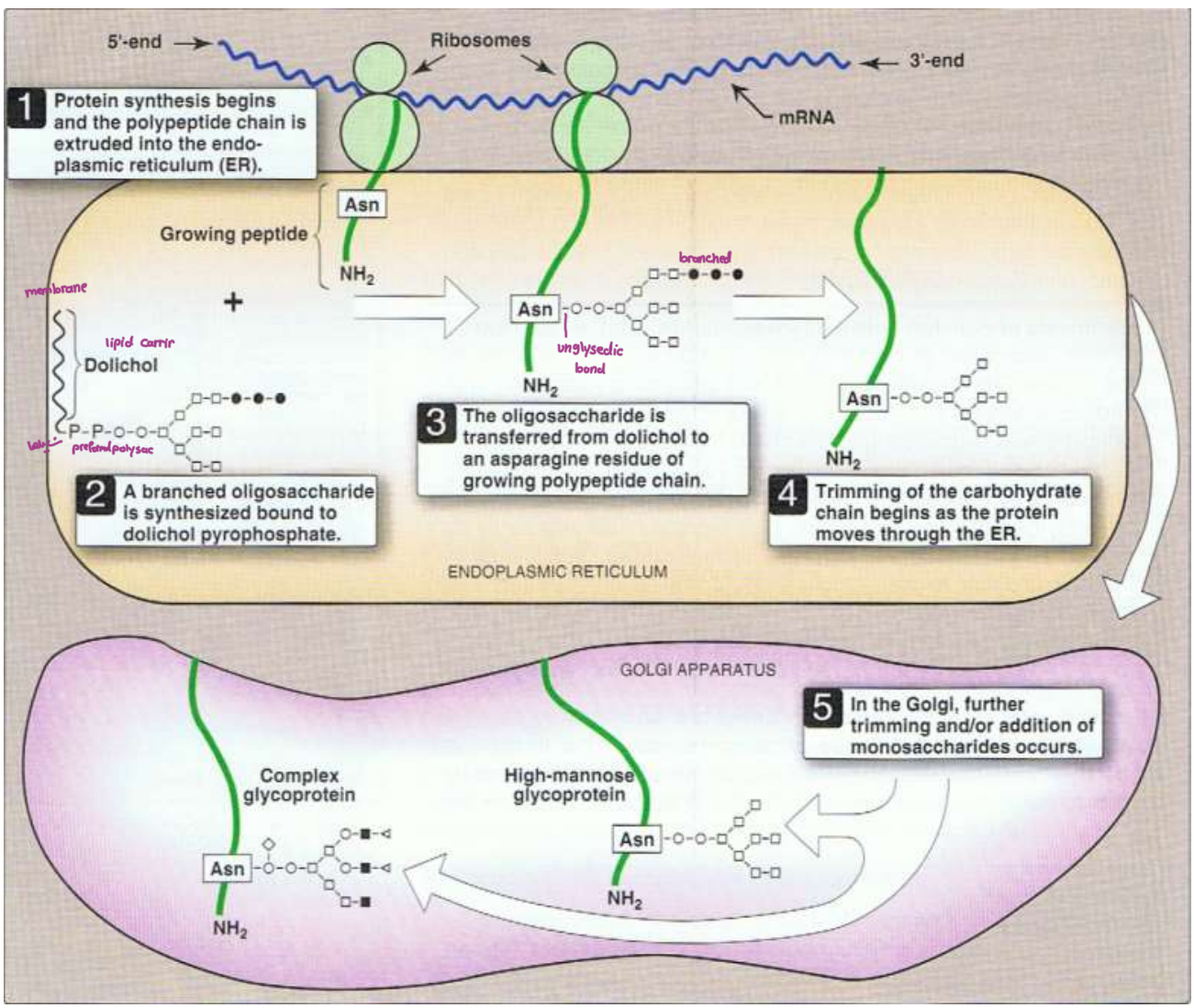
بشكل مبسط:

- البروتينات السكرية (glycoproteins) هي بروتينات مرتبطة بسلاسل من السكريات.
- هذه السكريات لا تُضاف مباشرة من السكر الخام، بل من مركبات تسمى **"نوكليوتيدات السكر" (sugar nucleotides)**.
- نوكليوتيدات السكر هي مركبات تتكون من **سكر مرتبط بنوكليوتيد** (مثل UDP-glucose، GDP-mannose، إلخ)، وتعمل كمصدر أو "مانح" للسكريات أثناء عملية بناء السلاسل السكرية على البروتين.

يعني: الجسم يستخدم هذه المركبات الوسيطة (نوكليوتيدات السكر) لبناء السكريات التي تضاف إلى البروتينات.

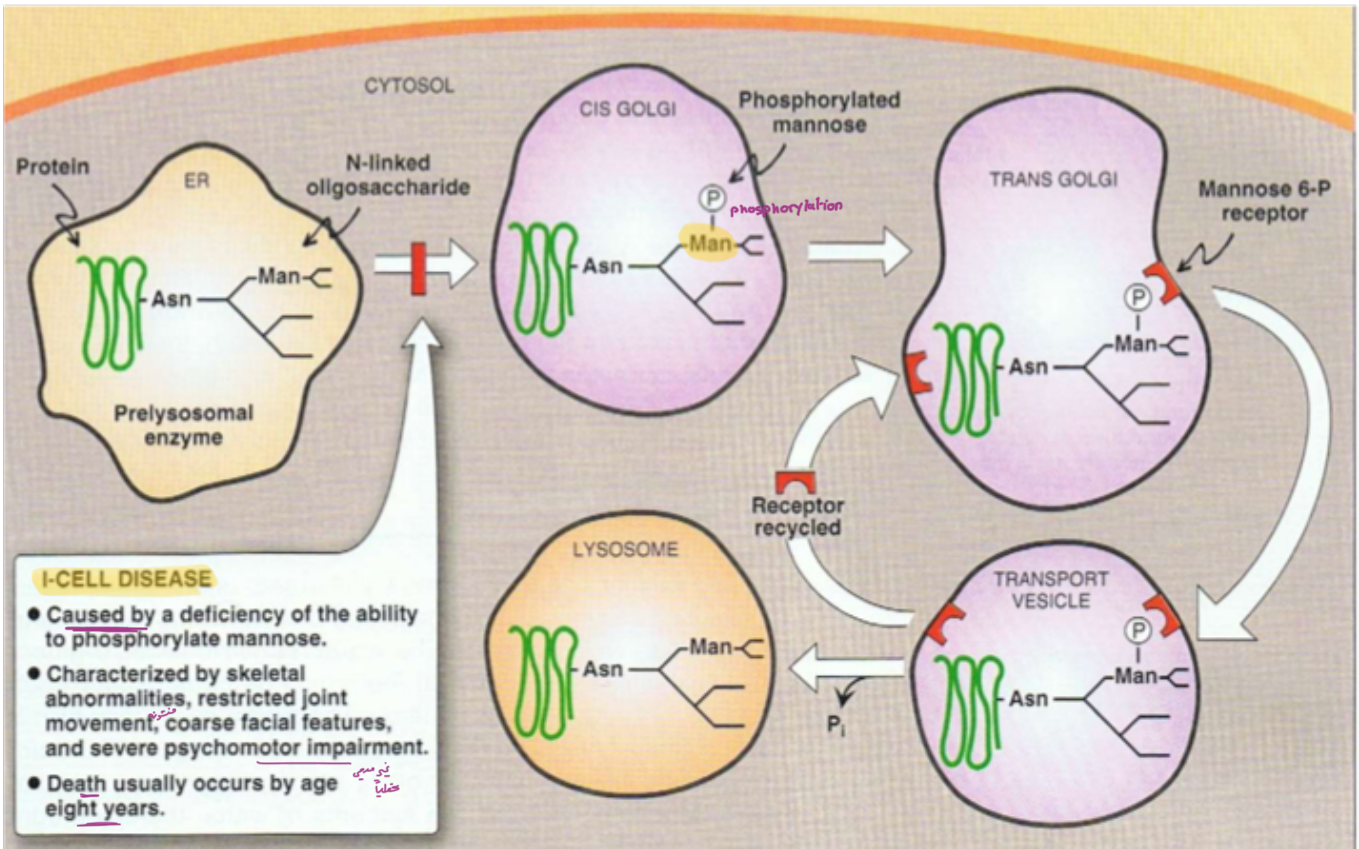

ROUGH ENDOPLASMIC RETICULUM (RER)
• Ribosomes are bound to the cytosolic side of the RER membrane.
• Protein-containing vesicles are sent to the Golgi for processing.
Ribosome
Secretory vesicle
Vesicles bud off from the Golgi, and their processed contents are targeted to the cell membrane, extracellular environment, or lysosomes.
GOLGI APPARATUS
Protein
Carbohydrate
Secretory vesicle
Lysosome
Secretory vesicle
Protein
Glycoproteins that are to be secreted from the cell are not incorporated into the vesicular membrane.
Carbohydrate
Protein
INTRACELLULAR SPACE
Cell membrane
EXTRACELLULAR SPACE
Glycoproteins that are to become components of the cell membrane are integrated into the membrane of the secretory vesicles that bud off from the Golgi and fuse with the cell membrane.
Carbohydrate

Synthesis of N-linked glycoproteins.



Lysosomal degradation of glycoproteins

- A deficiency in the phosphorylation of mannose residues in N-linked glycoprotein pre-enzymes destined for the lysosomes results in **I-cell disease**
- Glycoproteins are degraded in lysosomes by acid hydrolases
- A deficiency of one of these enzymes results in a glycoprotein storage disease (**oligosaccharidosis**), resulting in accumulation of partially degraded structures in the lysosome



Lipid metabolism

Lipid metabolism

- Lipids are water-insoluble organic molecules that can be extracted from tissues by nonpolar solvents
- Present as membrane associated, lipoproteins or droplets of triglycerides in adipose tissues
- They are the major source of energy
- Responsible for dissolving fat-soluble vitamins which have regulatory or coenzyme functions in the body
- Prostaglandins and steroid hormones play role in body‘s homeostasis

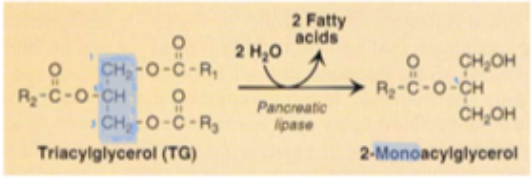
Lipid digestion

- An adult ingest 60-90 g of fat /day, 90% as triglycerides and the rest as cholesterol, phospholipids and free fatty acids.
- Digestion starts in stomach by lingual lipase and gastric lipase
- Triglycerides of short and medium chain length fatty acids (<12C) are the target of these enzymes.
- The enzymes are important in neonates to digest fat in milk and for people with cystic fibrosis (no pancreatic lipase)
- Emulsification of dietary lipid occurs in duodenum in presence of bile salts and perstalsis which will increase the surface area of digestion
- Bile salts are produced in liver and stored in gallbladder

Degradation by pancreatic enzymes

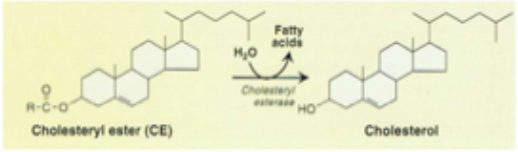
❑ Triacylglycerol degradation:

- ❑ Degraded by pancreatic lipase to 2-monoacylglycerol and free fatty acids
- ❑ Colipase (activated by trypsin) binds to the lipase in ratio 1:1 and anchors it to the lipid-aqueous interface
- ❑ Orlistat (antiobesity drug) inhibits gastric and pancreatic lipase and so decrease the absorption of fat



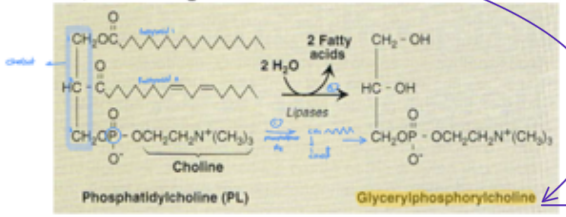
❑ Cholesteryl ester degradation:

- ❑ 10-15% of cholesterol is present in esterified form
- ❑ It is hydrolyzed by pancreatic cholesterol esterase to cholesterol and free fatty acids
- ❑ The activity of the enzyme is increased in the presence of bile salt



❑ Phospholipid degradation (like phosphotidylcholine):

- ❑ Degraded by **phospholipase A2** in presence of bile salts by removal of one fatty acid from C2 of PL to form lysophospholipid
- ❑ Lysophospholipid is hydrolyzed by **lysophospholipase** leaving free fatty acid and glyceryl phosphoryl base that can be excreted in feces, further degraded or absorbed



Control of lipid digestion

- It is hormonally controlled
  1. Cholicystokinin (CCK) which is secreted from the mucosa of jejunum and lower duodenum and acts on:
     a. Gallbladder to release bile
     b. Pancreas to release pancreatic enzymes
     c. Decrease gastric motility and so decrease gastric emptying

  2. Secretin which is secreted by other intestinal cells in response to the lower pH of the chyme cause pancreas and liver to release bicarbonate which will neutralize the pH making it optimum for the pancreatic enzymes to work

Absorption of lipids by intestinal mucosal cells

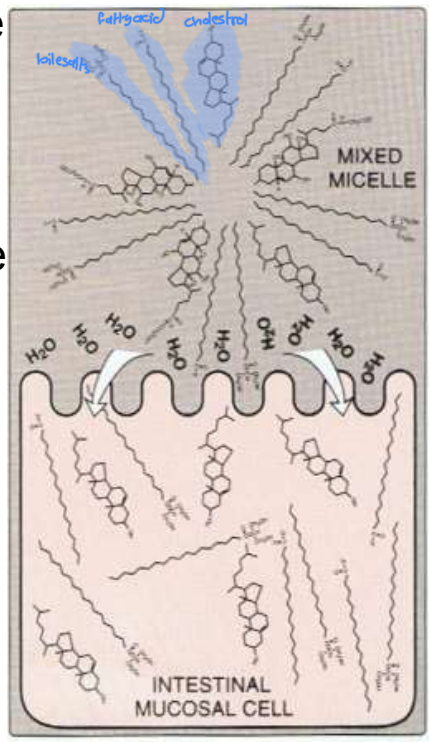
- The degradation products of lipids together with bile salts form mixed micelle (hydrophobic inside and hydrophilic outside)

(to be able to cross the water layer)

(OH)

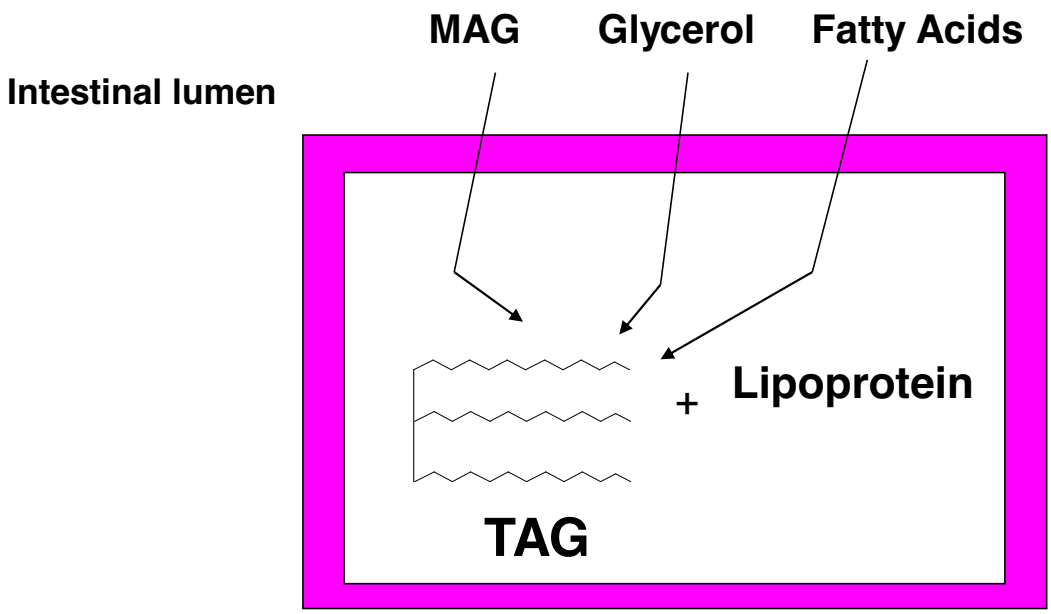
- The hydrophilic surface facilitate the transport of the hydrophobic lipids through the unstirred water layer (ثابتة) to the brush boarder membrane where they are absorbed.

- Formation of mixed micelles is not required for the absorption of short and medium chain length fatty acids → can cross easily without it



Absorption of lipids by intestinal mucosal cells

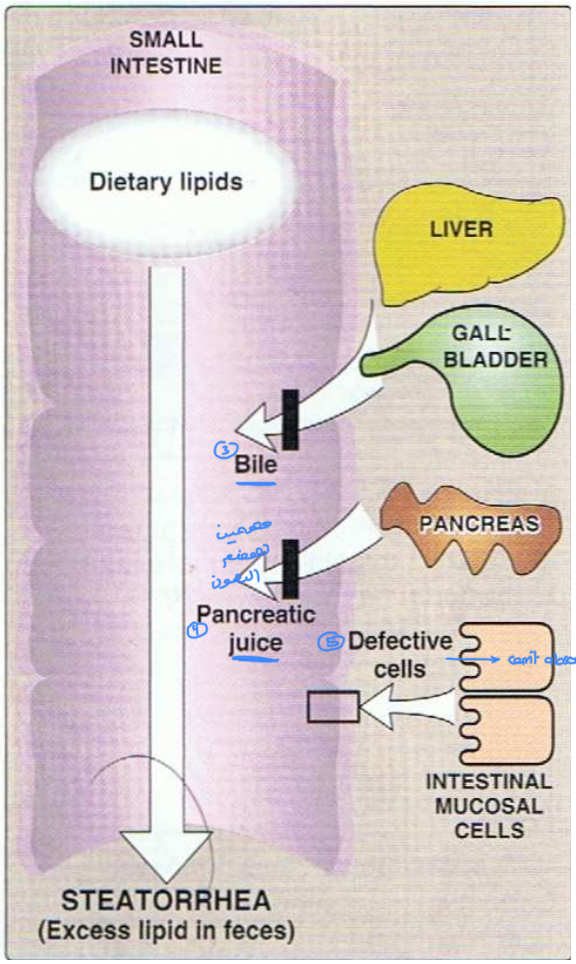
- In enterocytes triacylglycerol and cholesteryl esters are resynthesized
- Short and medium chain length fatty acids are not converted to their CoA derivatives but released into portal circulation and carried by serum albumin to the liver to be metabolized.



Lipid malabsorption (Steatorrhea)

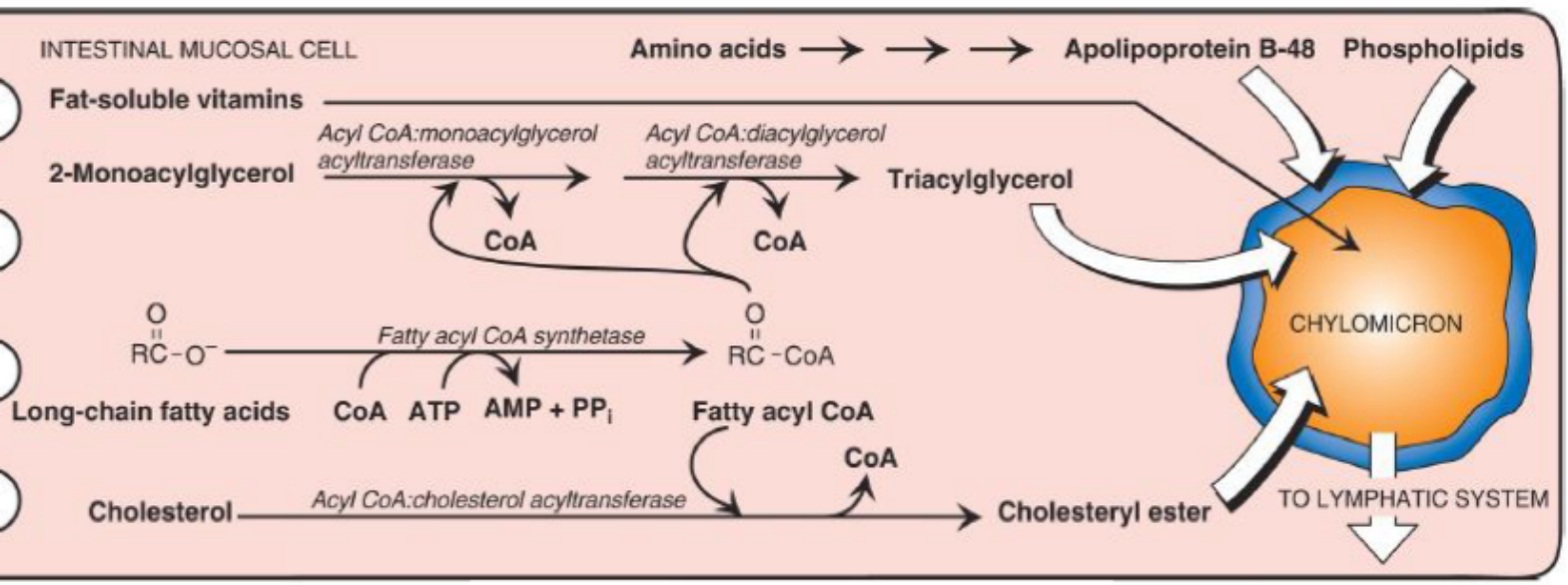
1. Cystic fibrosis → no pancreatic lipases → no enzymes
2. Shortened bowl تقص المعده

- Both causes decrease in absorption of lipids (including fat soluble vitamins and essential fatty acids) leading to increase in lipids in feces (Steatorrhea)



Secretion of lipids from enterocytes

- Phospholipids, unesterified cholesterol, and (apolipoprotein B-48) are at the outer layer and triacylglycerol and cholesterol ester form chylomicrons. And this is released to the chyle (milky appearance)
- This is released to blood



شرح مبسط:

- الكيلوميكرونات (Chylomicrons) هي جزيئات كبيرة تحمل الدهون من الأمعاء إلى باقي الجسم.
- **مِمَّا تتكوّن؟**
  - **الطبقة الخارجية**: فيها
    - فوسفوليبيد (phospholipids)
    - كوليسترول غير مسترف (unesterified cholesterol)
    - بروتين اسمه **Apolipoprotein B-48**
  - **الداخل**: يحتوي على
    - دهون ثلاثية (triacylglycerol)
    - كوليسترول استيري (cholesteryl ester)
- لما تتركب هاي الكيلوميكرونات في الخلية، يتم إطلاقها في سائل اسمه **الكايل (chyle)**، وهو سائل شكله **لبني** لأنه غني بالدهون.
- بعد هيك، تنتقل إلى **الدم**.

Use in tissue

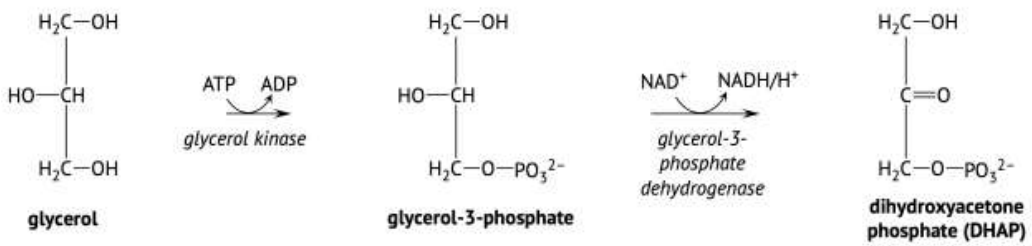
- Triacylglycerol is broken down primarily in the capillaries of skeletal muscle, adipose tissues, heart, lung, kidney, and liver.
- Triacylglycerol in chylomicrons is degraded to free fatty acids and glycerol by lipoprotein lipase. This enzyme is synthesized primarily by adipocytes and muscle cells.
- Familial lipoprotein lipase deficiency (type I hyperlipoproteinemia) is a rare, autosomal recessive disorder that results from a deficiency of lipoprotein lipase or its coenzyme, apo C-II. The result is massive chylomicronemia.

Fate of free fatty acids

1. The free fatty acids derived from the hydrolysis of triacylglycerol may directly enter adjacent muscle cells or adipocytes
2. The free fatty acids may be transported in the blood in association with serum albumin until they are taken up by cells.
3. Most cells can oxidize fatty acids to produce energy
4. Adipocytes can also reesterify free fatty acids to produce triacylglycerol molecules, which are stored until the fatty acids are needed by the body.

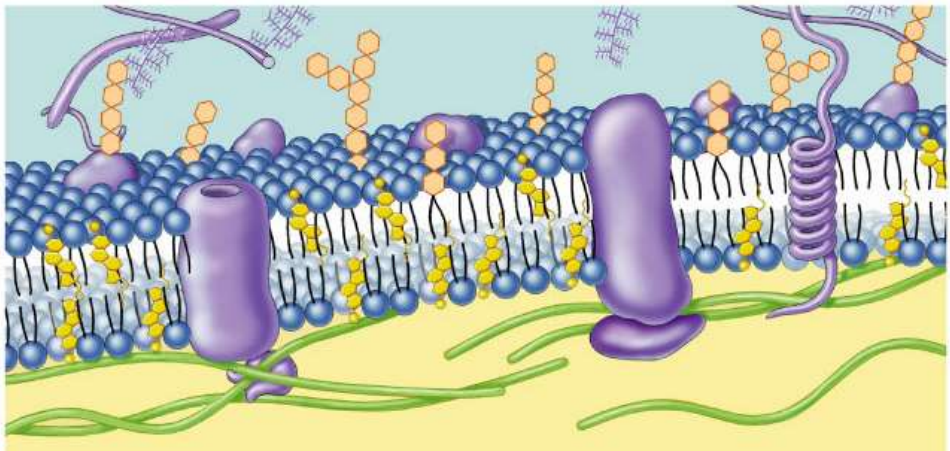
Fate of glycerol

- Glycerol that is released from triacylglycerol used almost exclusively by the liver to produce glycerol 3-phosphate, which can enter either glycolysis or gluconeogenesis by oxidation to dihydroxyacetone phosphate



glycerol → (glycerol kinase) → glycrol-3-phosphate → (oxidation by glycerol phosphate dehydrogenase) → Dihydroxy acetone phosphate

Cell membrane

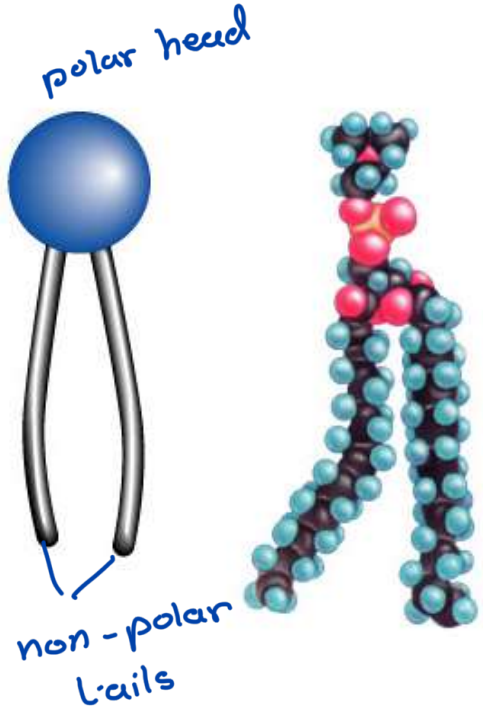


Function of the cell membrane

- Separation of the cell components from the nonliving surroundings (8 nm thick)
- It controls traffic into and out of the cell.
- Like other membranes, the plasma membrane is **selectively permeable**, allowing some substances to cross more easily than others (hydrophilic vs hydrophobic)

Composition of cell membrane

- The basic structural unit of biological membranes is a lipid bilayer
- Phospholipids are the primary bilayer forming lipids

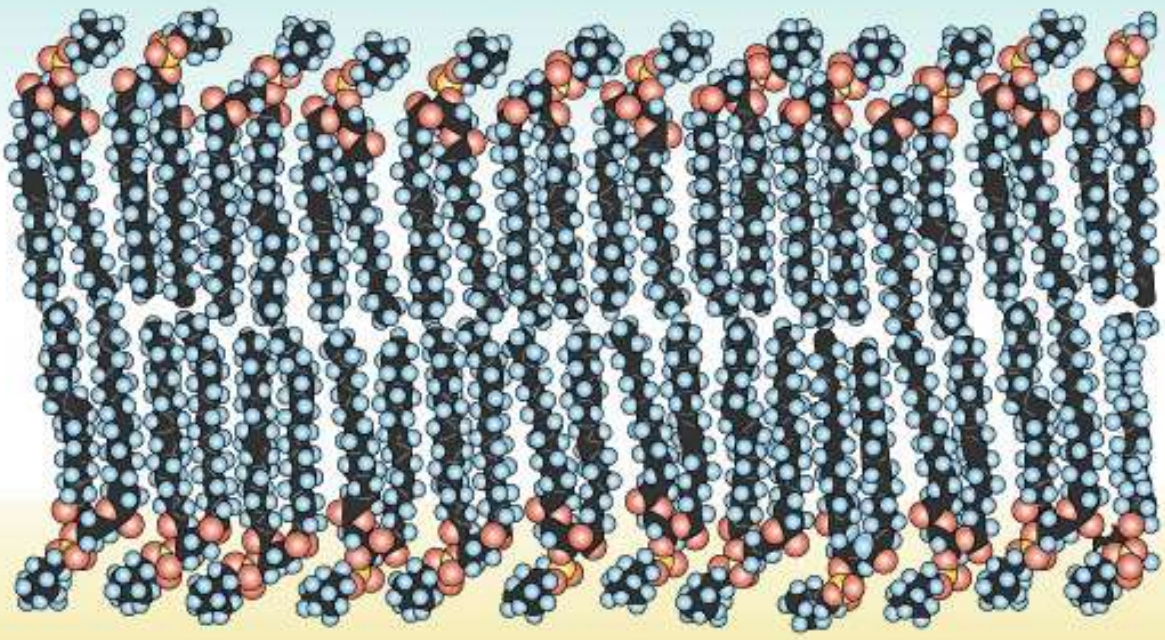


General membrane structures

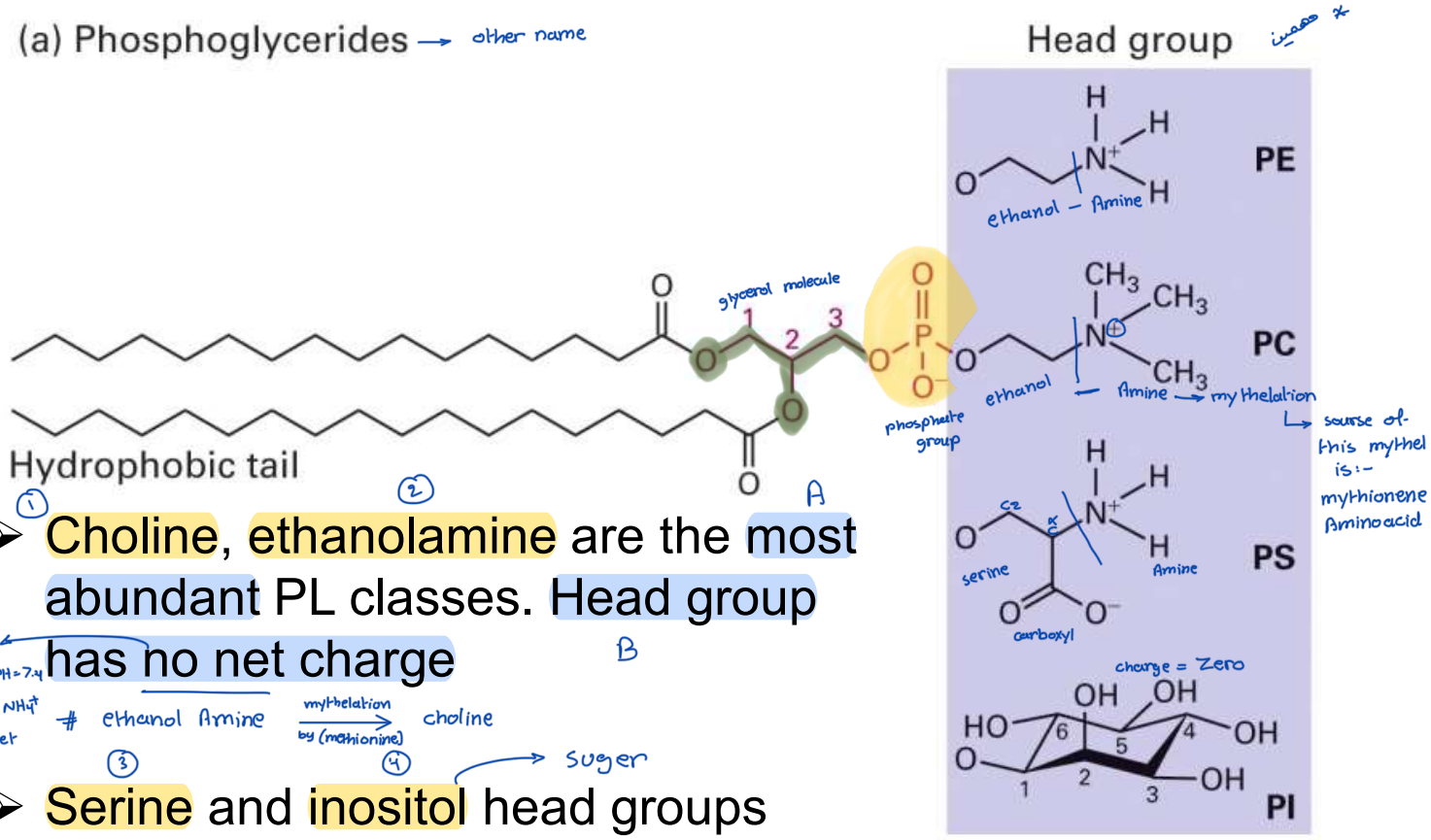
polar
hydrophilic
heads

nonpolar
hydrophobic
tails

polar
hydrophilic
heads



Different types of phospholipids



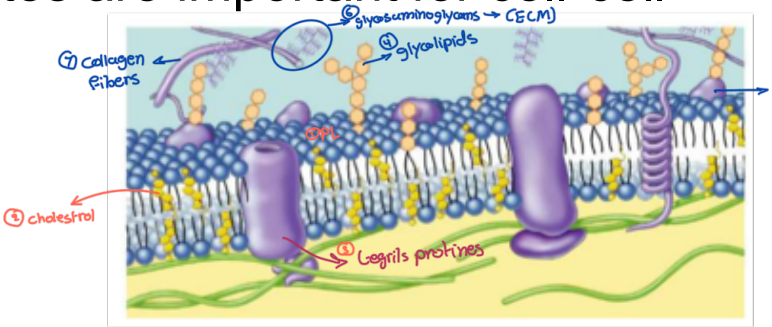
- Choline, ethanolamine are the most abundant PL classes. Head group has no net charge

- Serine and inositol head groups have net negative charges

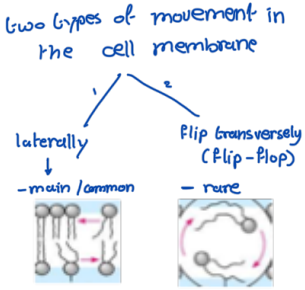
Characteristics of membrane

- The main macromolecules in membranes are lipids and proteins, but include some carbohydrates
- Membranes are fluid
- Membranes are mosaics of structure and function
- Membrane carbohydrates are important for cell-cell recognition

glycolipids / glycolipids



مهمة جدًا

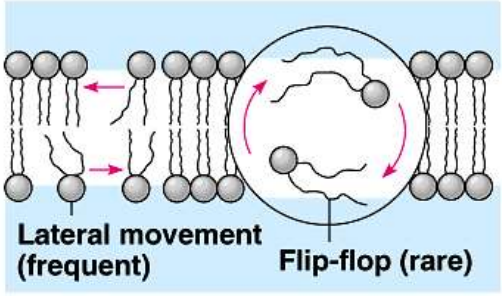


Membranes are fluid

- A membrane is held in together by weak **hydrophobic** interactions

- Most membrane lipids and some proteins can drift **laterally** within the membrane (2 microns per second)

- Molecules **rarely flip transversely** (flip-flop) across the membrane, because hydrophilic parts would have to cross the membrane's hydrophobic core.

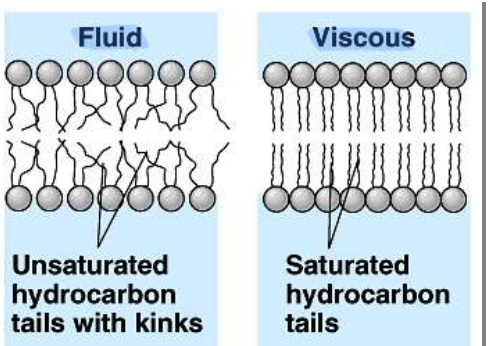


(a) Movement of phospholipids

Membranes are fluid

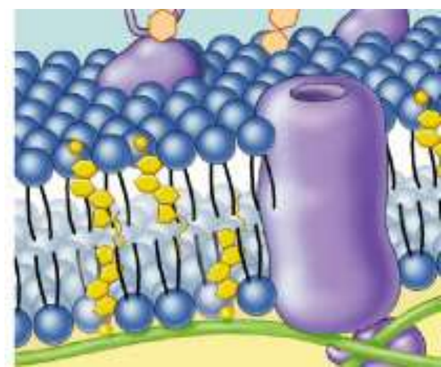
- Membrane fluidity is influenced by temperature and by its constituents.
- As temperatures cool, membranes switch from a fluid state to a solid state as the phospholipids are more closely packed.
- Membranes rich in unsaturated fatty acids are more fluid that those dominated by saturated fatty acids because the kinks in the unsaturated fatty acid tails prevent tight packing

kinks → prevent tihght packing



Membranes are fluid

- Short chain fatty acyl groups tend to increase lateral mobility
- cholesterol in membrane of eukaryotes, modulates **membrane fluidity** by making the membrane:
  - Less fluid at warm temperatures (e.g. 37 ^{o}C body temperature) by restraining the phospholipid movement.
  - More fluid at lower (cool) temperatures by preventing close packing of phospholipids.
  - Cells may **alter** membrane lipid concentration in response to changes in temperature



Membranes are mosaics of structure and function

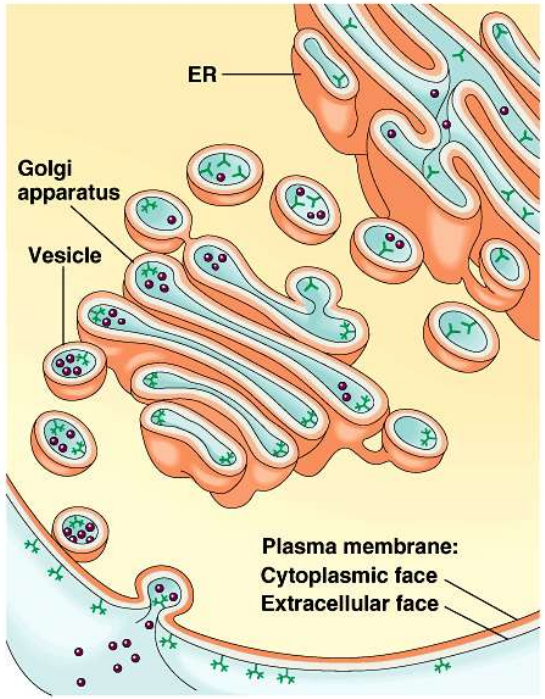
so many structures

توزع المواد من برا (شكلو) شي من جوا

- Membranes have **asymmetric** inside and outside faces. The membrane's synthesis and modification by the ER determines this asymmetric distribution of lipids, proteins and carbohydrates.
  - The two lipid layers may differ in lipid composition.
  - Membrane proteins have a clear direction.
  - When present, carbohydrates are restricted to the membrane's exterior

مواجهه إما ECM
ICM
مكان معين و ثابت

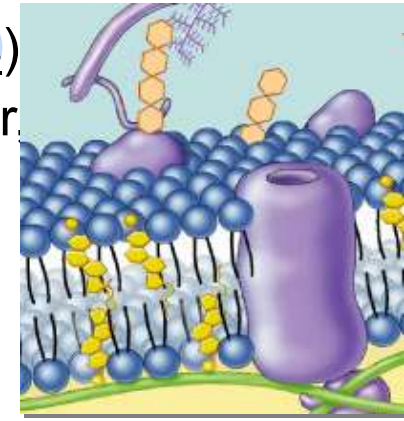
فقط من برا



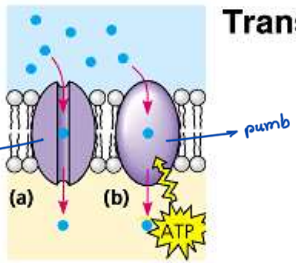
Membrane Proteins

- Proteins determine most of the membrane's specific functions

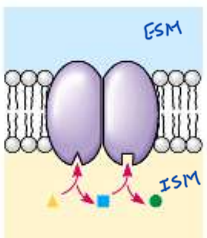
- Membrane proteins:
  - **peripheral proteins**
    - loosely bound to surface of membrane
    - cell surface identity marker (antigens)
  - **integral proteins:** penetrate lipid bilayer, usually across whole membrane
    - transmembrane protein:
      - transport proteins (channels, permeases (pumps))



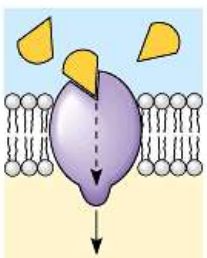
Many Functions of Membrane Proteins



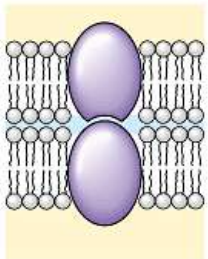
Transport



Enzymatic activity

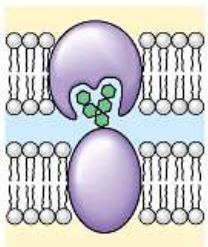


Signal transduction

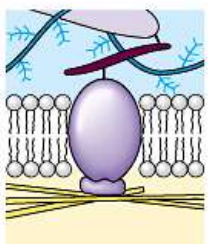


Intercellular joining

connection between cells



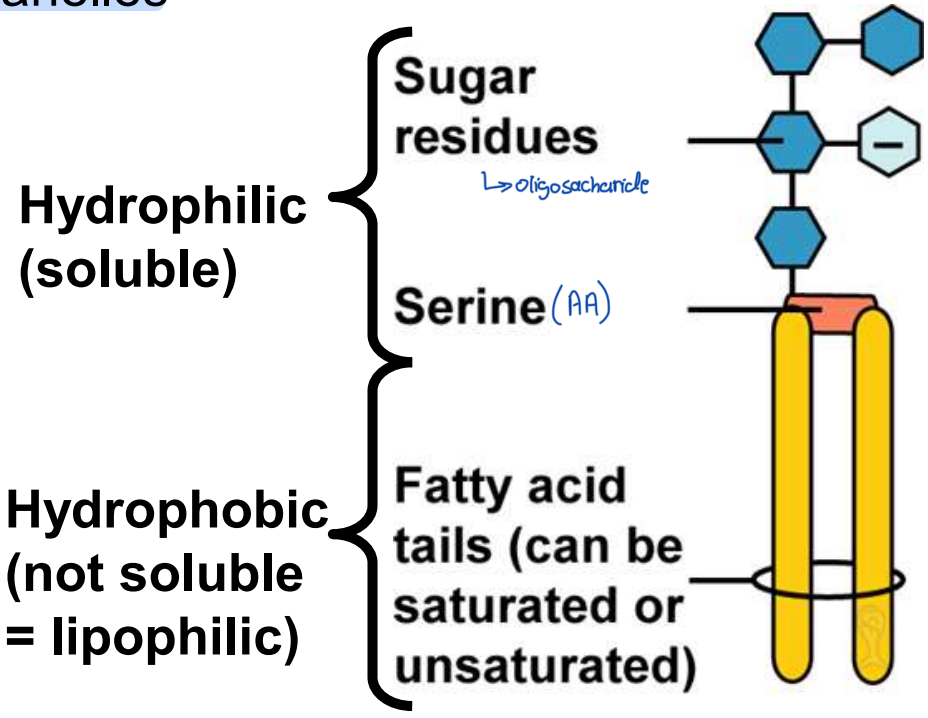
Cell-cell recognition



Attachment to the cytoskeleton and extracellular matrix (ECM)

Glycolipids

- Pattern of sugar residues is variable
- Always in outer leaflet of cell membrane, & inner leaflet of organelles



Membrane carbohydrates are important for cell-cell recognition

- Cell-cell recognition: The ability of a cell to distinguish one type of neighboring cell from another.

- Cell-cell recognition is crucial in the functioning of an organism. It is the basis for:
  - **Sorting** of cells into tissues and organs in an animal embryo's cell.
  - **Rejection** of foreign cells by the immune system.

- The way cells recognize other cells is probably by keying on surface molecules (**markers**)

Membrane carbohydrates are important for cell-cell recognition

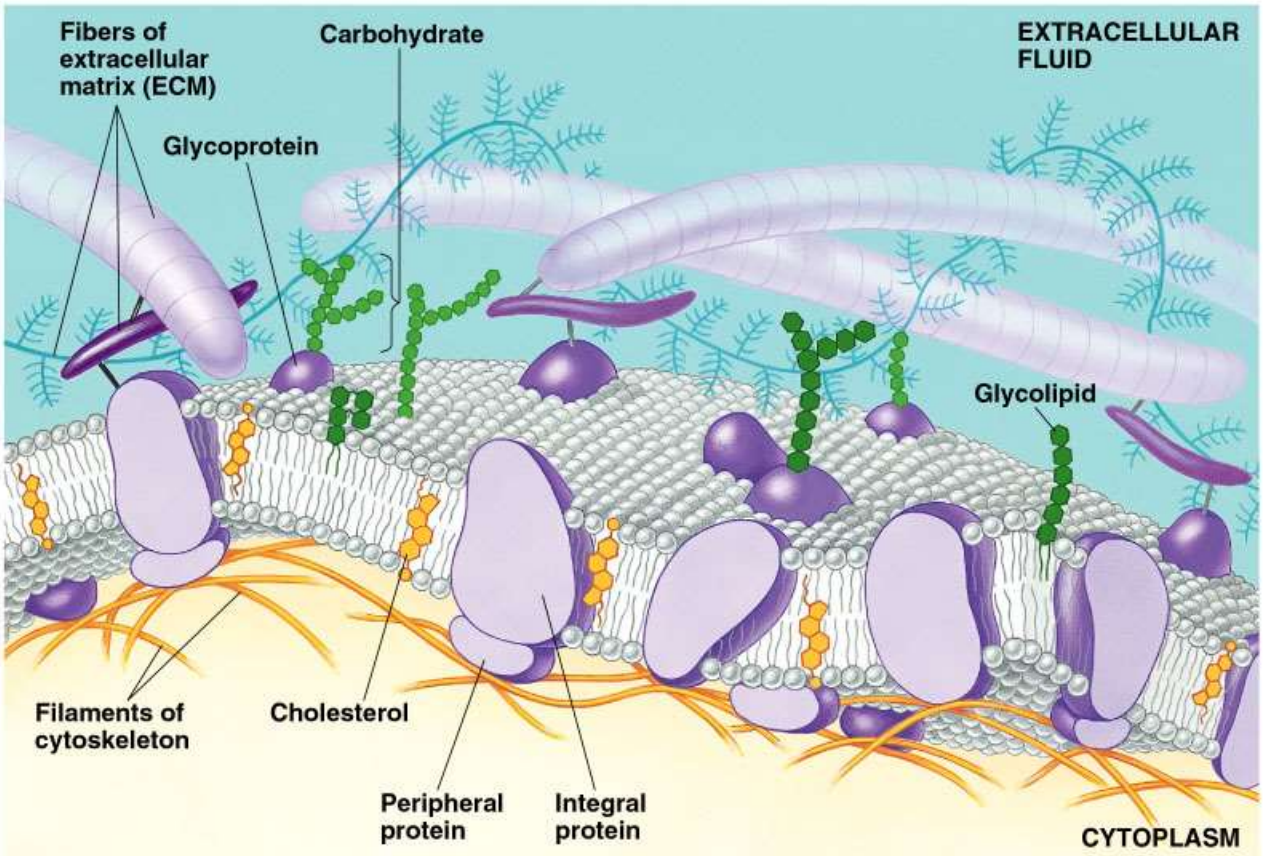
- Membrane carbohydrates are usually branched oligosaccharides with fewer than 15 sugar units.

- They may be covalently bonded either to lipids, forming glycolipids, or, more commonly, to proteins, forming glycoproteins.

carb → covalently bonded to
- lipids
- more common: proteins

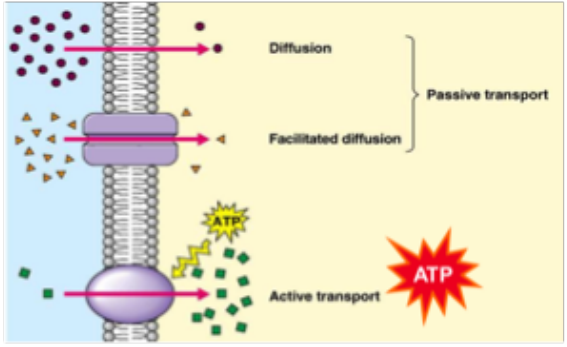
- The oligosaccharides on the external side of the plasma membrane vary from species to species, individual to individual, and even from cell type to cell type within the same individual

Movement across cell membrane



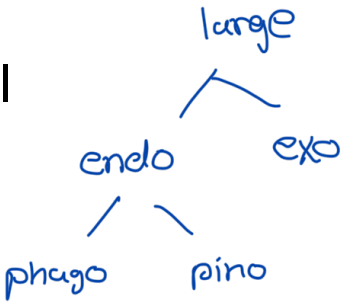
Movement across cell membrane

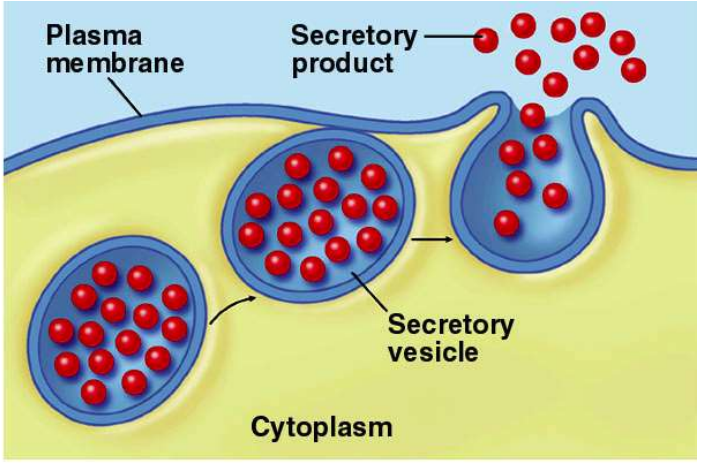
- **Passive Transport**
  - **Simple diffusion**
    - diffusion of nonpolar, hydrophobic molecules
      - lipids
      - high → low concentration gradient
  - **Facilitated transport**
    - diffusion of polar, hydrophilic molecules
    - through a protein channel
      - high → low concentration gradient
- **Active transport**
  - diffusion *against* concentration gradient
    - low → high
  - uses a protein pump
  - requires ATP



Transport of large molecules

- Moving large molecules into & out of cell
  - through vesicles & vacuoles
  - **endocytosis**
    - phagocytosis = “cellular eating”
    - pinocytosis = “cellular drinking”
  - **exocytosis**

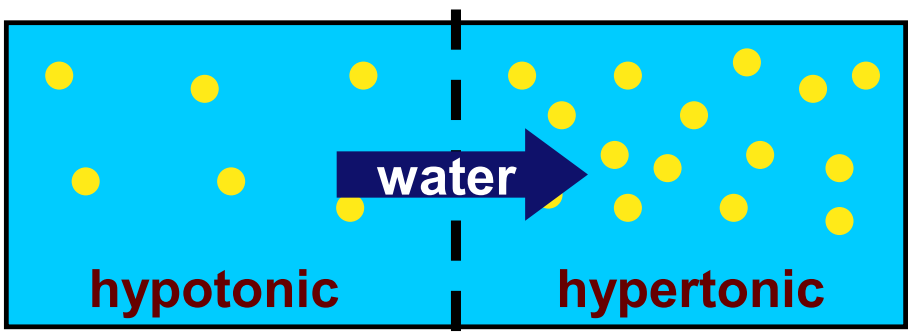




Diffusion of water

low of. solid → Hypo

- Diffusion of water from ***high concentration*** of water to ***low concentration*** of water high of solid → Hyper
- Direction of osmosis is determined by comparing total solute concentrations
  - Hypertonic - more solute, less water
  - Hypotonic - less solute, more water
  - Isotonic - equal solute, equal water



net movement of water