PASSION ACADEMIC TEAM

+

Sheet# 3

YU - MEDICINE

GASTROINTESTINAL SYSTEM

Lec. Title : Liver Metabolism Written By : Amira Otoum .

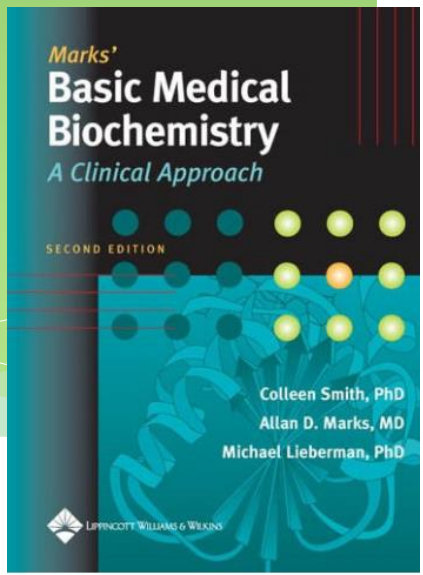
.

IF YOU COME BY ANY MISTAKE , PLEASE KINDLY REPORT IT TO SHAGHAFBATCH@GMAIL.COM

2. Liver Metabolism

DONE BY : AMEERA OTOUM

You can always win , but don't be afraid of making decision ☺



why do we study this lecture??

* We will talk about liver metabolism ,because the next topic will be liver function and liver function test to determine if we have problem in the liver (liver disorders).
* In general ,we talk about our GIT and we know that the liver isn't a major one or part of digestive system (is accessory organ helps the digestive system to complete the digestion) ,that is why we interested in the liver and we are going to describe certain functions of the liver that are related to digestion process.

LIVER ANATOMY

* Two lobes, each containing multiple lobules and sinusoids.
* 75% of its blood supply from the portal vein

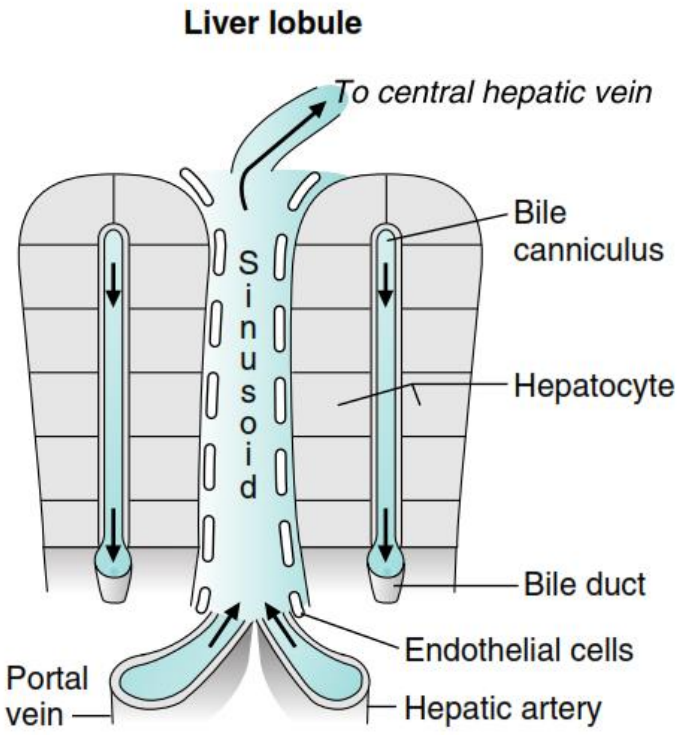


Fig. 46.1. Schematic view of liver anatomy.

LIVER CELL TYPES

A. Hepatocytes :

B. Endothelial Cells

C. Kupffer Cells

D. D. Hepatic Stellate Cells

E. E. Pit Cells

A. Hepatocytes (parenchymal cells):

I. 80 % of the liver volume

II. Almost all pathways of metabolism

III. Replaceable

B. Endothelial Cells:

I. lining cells of the sinusoid

II. They allow for free diffusion of small molecules to the hepatocytes but not chylomicrons-size

III. capable of endocytosing

IV. lack of tight junction

C. Kupffer **Cells** (tissue macrophages)

I. **Located within the sinusoidal lining**

II. **¼ of liver lysosomes**

D. Hepatic Stellate Cells (perisinusoidal or Ito cells)

I. **Lipid-filled cells (the primary storage site for vitamin A)**

II. **Involved in liver cirrhosis**

E. Pit Cells

I. liver-associated lymphocytes (are natural killer cell)

Note : all previous slides are not important for our exam regarding to biochemistry questions as the doctor says ,but for us to refresh our information .

But the next slides are so important so be alert ☺

MAJOR FUNCTIONS OF THE LIVER

MAJOR FUNCTIONS OF THE LIVER

A. The Liver Is a Central Receiving and Recycling Center for the Body.
-because the portal system is responsible for transportation for all entrance molecules to the body that we absorb them through GIT

B. Inactivation and Detoxification of Xenobiotic Compounds and Metabolites .
- so we have huge numbers of molecules and we can't imagine that how many molecules introduced to our body that need to be detoxified or inactivated in order to avoid certain drastic conditions that could be developed in our body so it is very important to be inactivated and this function will be performed by our cytochrome system that we have in the liver .

*if we go through the story of cytochrome system in our liver cells ,this amazing mechanism for detoxification, tell us that we are already designed for non formed molecules not formed molecules or compounds ??

What that's mean ?

Due to the development of technology and biotechnology ,each day we have new compounds and structures and the simplest example is drugs (we called them Xenobiotic)→these compounds that we synthesis them by chemical ways can be detoxified and recognized by our cytochrome system .

So our systems are designed to face unknown molecules so it is an definitive evidence of evolution theory (this theory because of the process of exposures or the process of neglecting something)

يعني نظرية التطور بتحكي انو احنا نتيجة استخدامنا لاشياء وتعرض لمحفزات حيوية خلتنا نعمل اشياء معينة في اجسامنا او الكائنات تعملها بطريقة لا ارادية او ارادية (مش معروف شو قصدهم بكلمة ارادية ونعمل عملية metabolism of molecules ما كانوا موجودين قبل بالتالي can't be explained by evolutions يعني كيف تطورنا لاشي مش موجود اصلا؟ .

*in the future we will develop other kinds of molecules and toxic metabolites that will be metabolized by our cytochrome systems

SO CYTOCHROMES ARE THE GUIDE FOR THE GOD (دليل وجود الله)

C . Regulation of Blood Glucose Levels (HOMESTASIS)

- by gluconeogenesis or glycogen lysis or glycogen synthesis.

D . Synthesis and Export of Cholesterol and Triacylglycerol(lipids)

- because it is responsible for the formation of VLDL .

*كل الليبيدات يلي بنمتصهم من الغذاء بنعمللهم عمليات هضم وبضل منهم بقايا هذول البقايا بالدورة الدموية بروحوا باتجاه الكبد والكبد مسؤول عن ال recycling of these molecules and exporting them as a new structures called LVDL

E . Ammonia and the Urea Cycle

- We will convert the ammonia into urea to be less toxic

F . Ketone Body Formation

- Because ketones are very important for certain kind of tissues during starvation like CNS

G . Nucleotide Biosynthesis

-it is very necessary thing that we have to build in our body (adenosine ,guanine, cytosine , thymine also with ribose and phosphate group →they are called nucleotides)

H . Synthesis of Blood Proteins

-for example alpha 1 antitrypsine

I . The Synthesis of Glycoproteins and Proteoglycans

- that can be used by other types of tissues

J . The Pentose Phosphate Pathway

- which is responsible for metabolism of glucose to produce NADPH molecules as a reducing agents for the anabolism.

FUELS FOR THE LIVER

Consumes approximately 20% of the body oxygen (huge amount of o2)→mean that liver do a lot of functions .

The principle forms in which energy is supplied

***these molecules can be generated by the liver or other types of cells as energy currency (mean we can use these molecules in order to catalyze certain reactions because they are energy currency molecules)**

Note : however , reduced NADPH isn't an energy currency ,but it is synthesized by the liver as well as Acyl-CoA thioesters.(these two molecules are helping in the anabolism)

1. Adenosine triphosphate (ATP).

2. Uridine triphosphate (UTP),.

3. Guanosine triphosphate (GTP).

4. Reduced NADPH.

5. Acyl-CoA thioesters.

Note : first three molecules are energy currency and the remainder two molecules are reducing agents ,but all of them (these five molecules) responsible of anabolism in the liver .

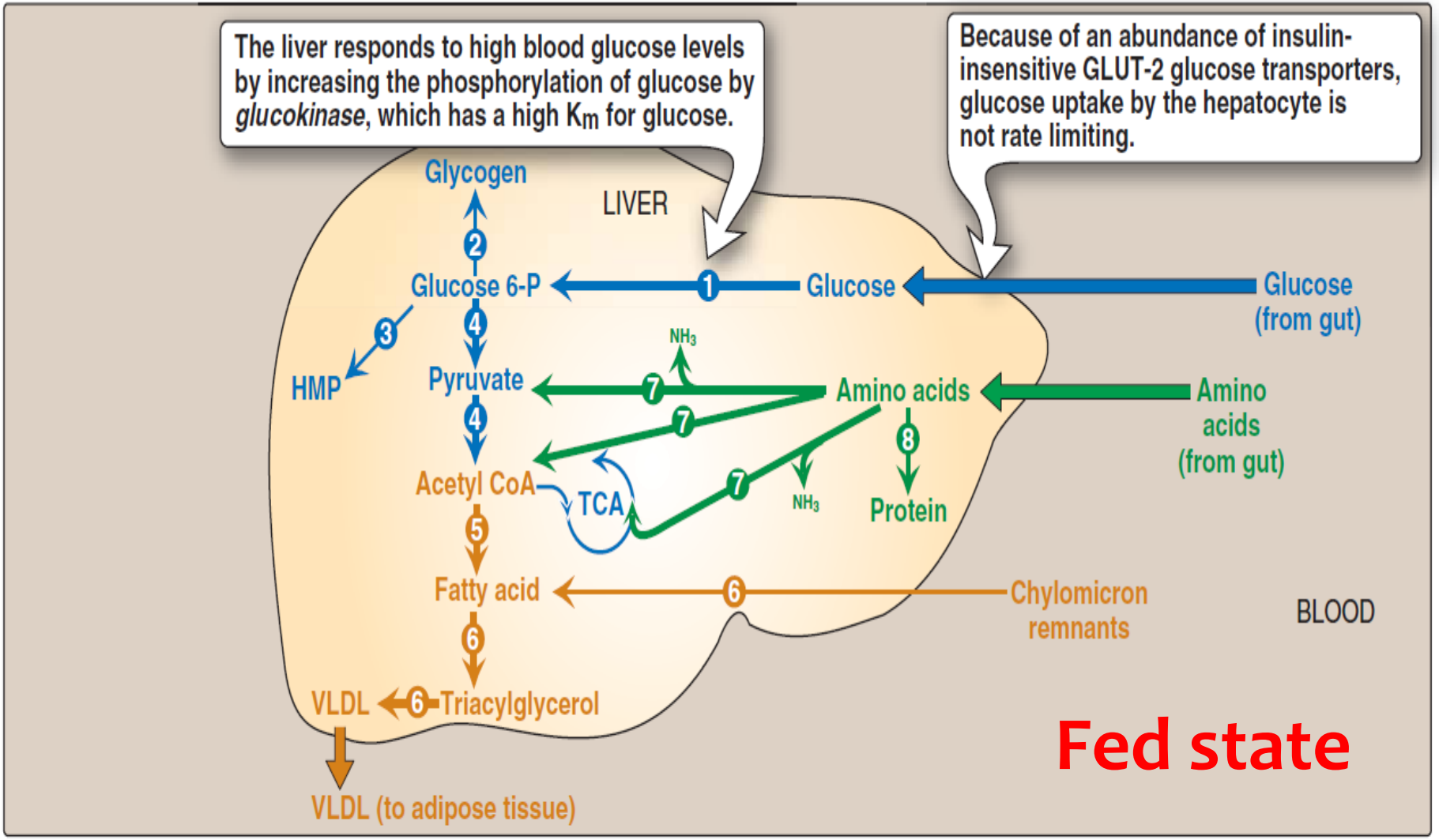


Figure 24.3

Major metabolic pathways in liver in the absorptive state. [Note: The acetyl CoA is also used for cholesterol synthesis.] The numbers in circles, which appear both in the figure and in the text, indicate important pathways for carbohydrate fat, or protein metabolism. **Blue text** = intermediates of carbohydrate metabolism; **Brown text** = intermediates of lipid metabolism; **Green text** = intermediates of protein metabolism.

شرح الصورة السابقة :

* According to metabolism liver has two status :

1)Well fed state (there is nutrients(diet state))

2)Starvation state

So if we classify these processing according what we will say ,will be more much easier to understand the function of the liver

*in fed state the blood is going to supply the liver by these two molecules (glucose from carbohydrate and amino acids from proteins) also chylomicron (from lipids after digestion by our digestive system or our cells we will have remnant)

*so basically ,

GLUCOSE :

1)glucose is going to be converted to glycogen (because we have well fed state so the glycogen synthesis is going to be active)

2) as well as we have glycolysis process (this is important and amazing that we have anabolism and catabolism and we will understand why is that)

3)as well as HMP(hexose monophosphate pathway , it is another mechanism for NADPH generation because the NADPH is very important for the anabolism))

Note ; our cells either do catabolism or anabolism ,while the liver has these two options

* AMINO ACIDS:

1)The amino acids either will converted to proteins (which are an important future source to produce VLDL)

2)Some of these amino acids are will going to metabolize to produce certain metabolites (some hormone or other forms of amino acids) and due to this it will release ammonia and these ammonia molecules need to be detoxified by ammonia cycle

3)And some of the amino acids can be degraded to produce acetyl CoA or pyruvate or certain components of the krebs cycle due to digestion

* And eventually the carbohydrate molecules and amino acids will be converted to fat ,why ? Because we have oxidation of acetyl CoA
* And why we are generating fats in the liver ?

Because one of the major functions of the liver is to produce fats to fuel the body with energy

So as a result we will use all of these component to produce fat as well as the glycogen synthesis

- These fat will exported as VLDL and then will be sent to the adipose tissue .

*so in general consumption of these molecules will cause obesity in the future by the help of liver itself (because liver cause metabolism of these molecules)

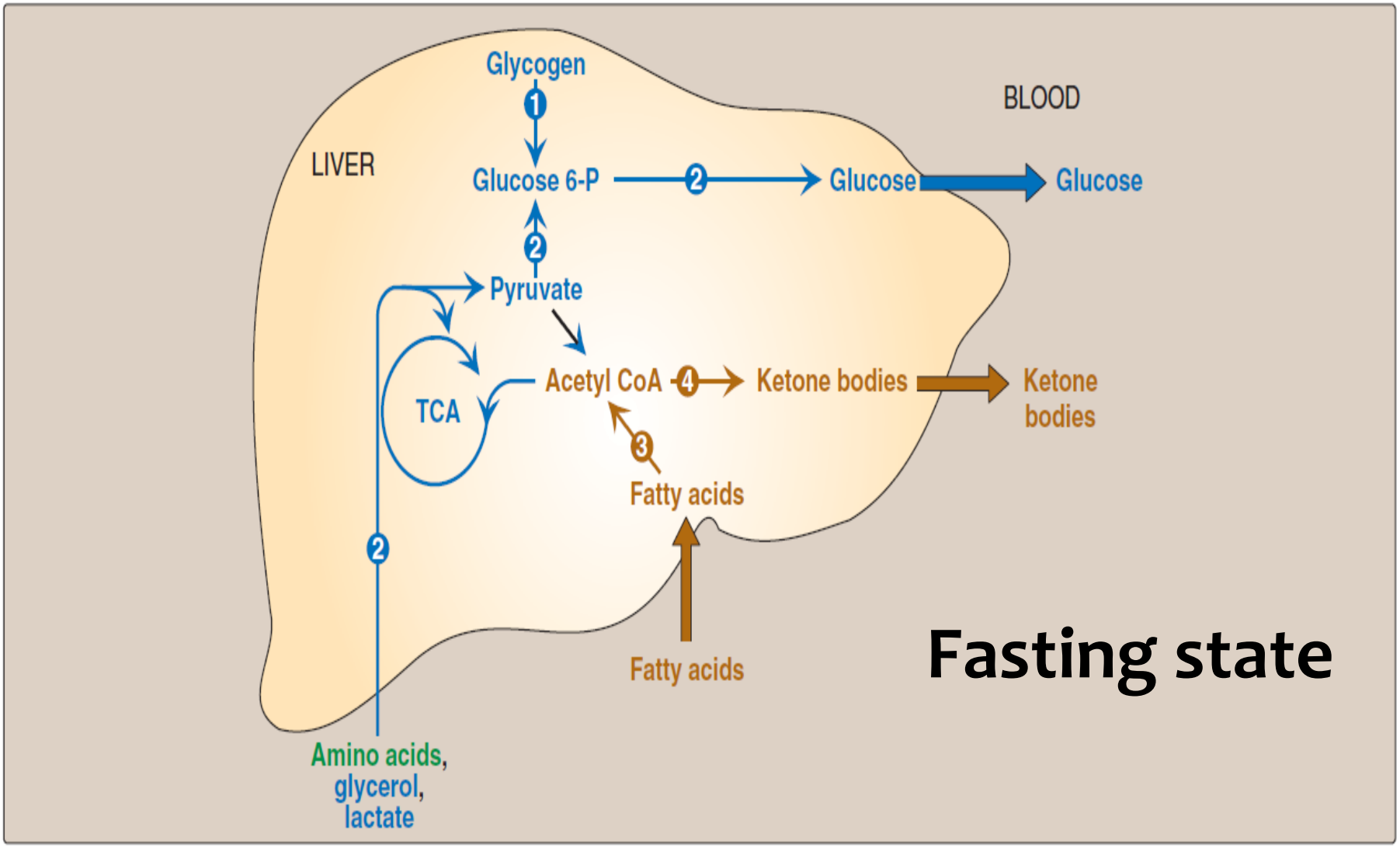


Figure 24.11

Major metabolic pathways in liver during starvation. [Note: The numbers in circles, which appear both in the figure and in the corresponding citation in the text, indicate important metabolic pathways for carbohydrate or fat.]

شرح السلايد السابق :

*in other hand we have fasting state or starvation state:

1) so we are going to consume our glycogen to produce glucose ,as well as we have to do gluconeogenesis so we have catabolic pathway and anabolic pathway (opposite of the well fed state),but still the liver can do anabolism and catabolism in order to produce glucose molecules for other tissues to preserve these tissue

2)The pyruvate molecules that is going to converted from your amino acids which are basically presents in solutions due to digestion of lipids in our body (because during starvation we start to break down our lipids and generate these molecules (glycerol and lactate) and these molecules are going to converted to pyruvate and acetyl CoA and eventually we will generate ketone bodies and these ketone bodies during starvation is very important)

Note :

- الدهون يلي بنحطمها في حالة ال starvation هي يلي جوا الجسم مو يلي من ال diet
- At the result ,all of these component are going to supply the production of either the glucose or ketone bodies ,why we are important to synthesis these molecules during fasting ?

Because these molecules are very important for certain types of tissues ,specifically nerve cells ,they rely on and can use ketones as well as glucose.

But ,When there is fasting and after a period of time ,glucose will be decreased ,so they will rely on ketones bodies which are produced due to accumulation of acetyl CoA accumulation due to fat digestion

* We will talk about the accessory organs that is associated with the digestive system and the most important one is the liver so we will talk about specific issues about the liver (metabolism of macromolecules)

A. Carbohydrate Metabolism in th Liver

Table 46.4. Major Fates of Carbohydrates in the Liver

- Storage as Glycogen
- Glycolysis to pyruvate
  - Followed by oxidation to carbon dioxide in the TCA cycle
  - Precursors for the synthesis of glycerol-3-phosphate (the backbone of triacylglycerols and other glyceolipids), sialic acid, and serine
  - Entry into the TCA cycle and exit as citrate, followed by conversion to acetyl CoA, malonyl CoA, and entry into fatty acid synthesis and secretion as VLDL
    - Synthesis of phospholipids and other lipids from triacylglycerols
- Conversion to mannose, sialic acid, and other sugars necessary for the synthesis of oligosaccharides for glycoproteins, including those secreted into blood
- Synthesis of acid sugars for proteoglycan synthesis and formation of glucuronides
- Oxidation in the pentose phosphate pathway for the formation of NADPH (necessary for biosynthetic reactions such as fatty acid synthesis, glutathione reduction, and other NADPH-utilizing detoxification reactions)

* حكي الدكتور عن السلايد السابق :

* Storage as glycogen
* In liver ,there is glycolysis to produce pyruvate if we are talking about well fed state and conversion of carbohydrates to other types of carbohydrates or monosaccharides in order to face the demand of the body for these carbohydrate .
* synthesis of these sugars and proteoglycan (specific types of sugars) .
* Pentose phosphate pathways presents in all cells to produce NADPH which is required for many functions ,one of them is the anabolism or glutathione reduction in the future in order to face the oxidative stress that we could have in the body or in our cells

B. Glucose as a Fuel

* The Km for (GLUT2) and glucokinase is so high (approximately 10 mM).
* Note : we have GLUT2 transporter as abundant transporter in liver cells as well as glucokinase and they have approximately high KM value which mean that we are going to deal with high concentration of glucose (either GLUT2 or glucokinase).

* Glucose will enter after its concentration rises to 10 to 40 mM in the portal blood.(for example after meal)and it :

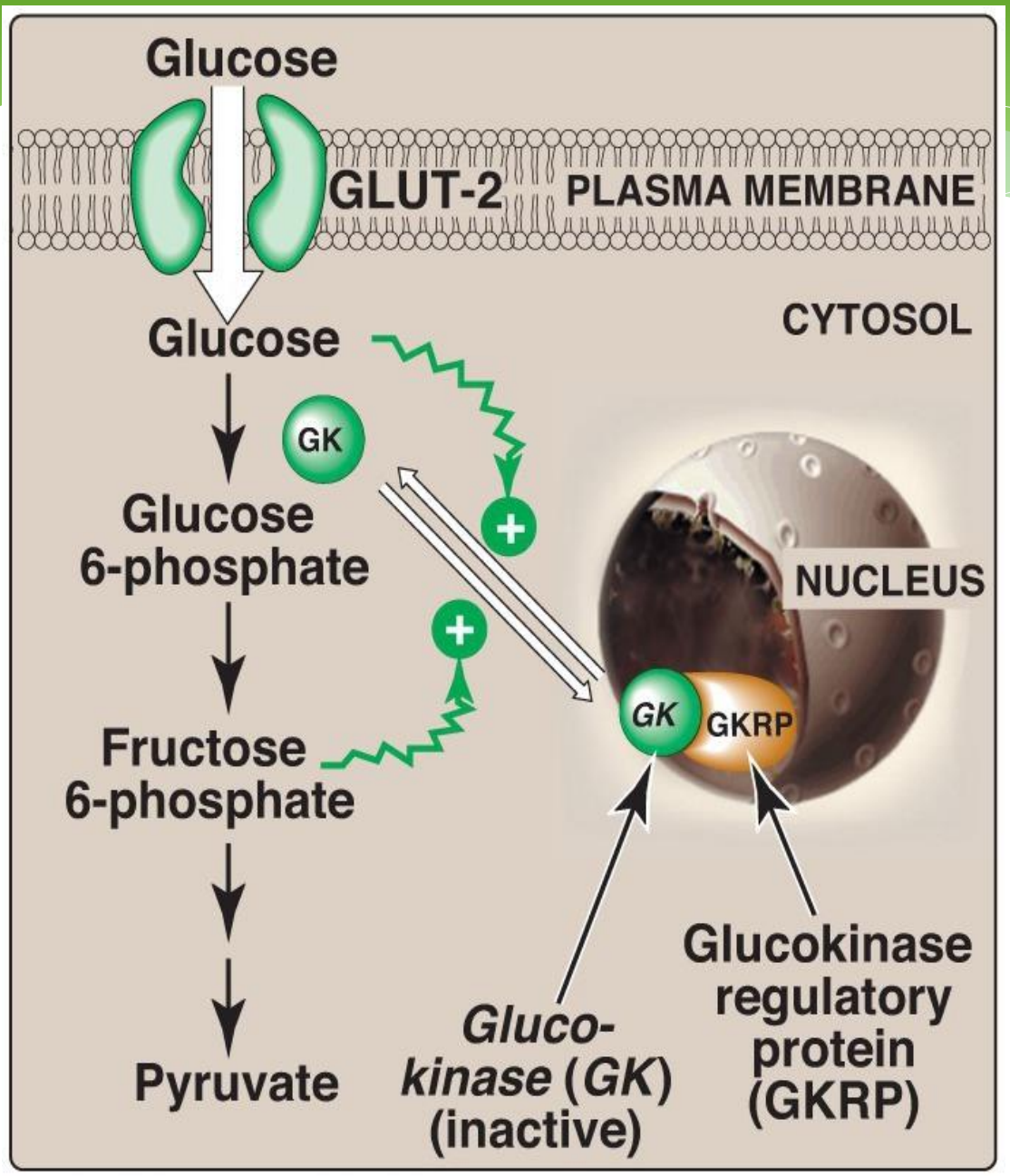
* 1)Glycogen synthesis will be increased

  or

* 2)Glycolysis will be increased as usual

  And

* 3)F. A. Synthesis will be increased(for certain extent) that is why we will form fat when we take carbohydrate



شرح السلايد السابق وهو بشكل عام بحكي عن احد خطوات ال regulation يلي بتصير اثناء عملية هضم الكربوهيدرات لانو هي عملية منظمة :

*after glucose inter by glut transporter (it happens in all cells ,but liver has special case Of metabolic point view),glucose continue in entering the cells until it reach to concentration equal to the external one ,we will face a problem of diffusion backward .

يعني بضل يدخل لجوا لحد ما يصير تركيزه جوا الخلايا يساوي تركيزه برا ولانه عملية النقل بهذا الناقل بتعتمد على ال concentration gradient رح يرجع ينتقل لبرا وهذا الاشي احنا ما بدنا اياه

*we want to keep glucose to be transported from the plasma or blood to cell and that is why glucose will be converted to another molecules in order to reduce the diffusion force (this force depends on concentration gradient because this transporter is concentration dependent transporter),and in order to do that we need certain enzymes which is irreversible enzyme that is known as glucokinase which belongs to a group of enzymes that known as hexokinases (enzymes that is responsible for conversion of glucose to glucose 6 phosphate and other carbohydrate as well) ,and glucokinase is a special type of hexokinases

*ملاحظة : ال glucokinase هذا مو specific للجلوكوز لا وانما هو بتعامل مع other hexose sugars

This enzyme (GK) do its role in regulation by localization → can be localized either in the cytosol or in the nucleus (can be localized in both directions)

*can be in the cytosol in its active form and transform the glucose to glucose 6 phosphate or in the nucleus and bind with regulatory proteins known as glucokinase regulatory proteins

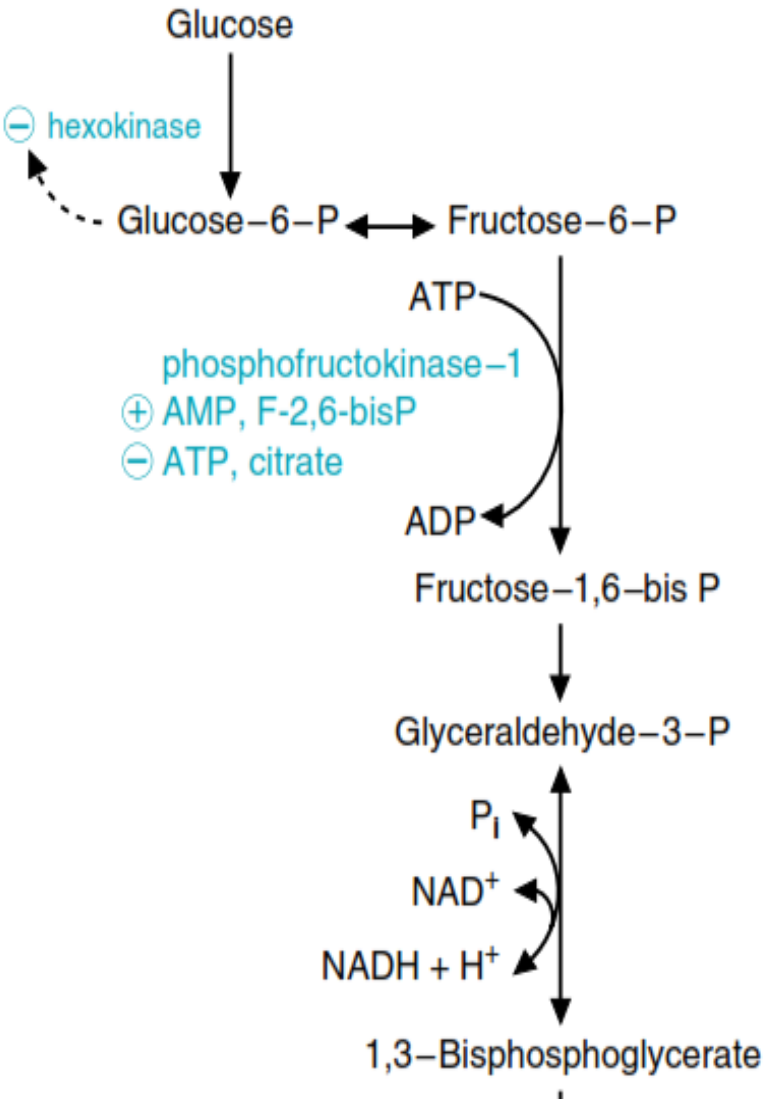
- This localization of GK depends on : 1) the concentration of glucose

2) Conversion of the glucose 6 phosphate to fructose 6 phosphate

These (1,2) are helping to convert the GK to the binding form and localized in the nucleus .

Note : the enzyme (GK) is always present

* **The major regulatory step for liver glycolysis is the PFK-1 step.**



* شرح السلايد السابق وهو بحكي عن خطوات اخرى لل regulation :
* Usually the regulation depends on phosphorylation or sometimes to feedback inhibition of certain products
* In glycolysis we have rate limiting stem is catalyzed by

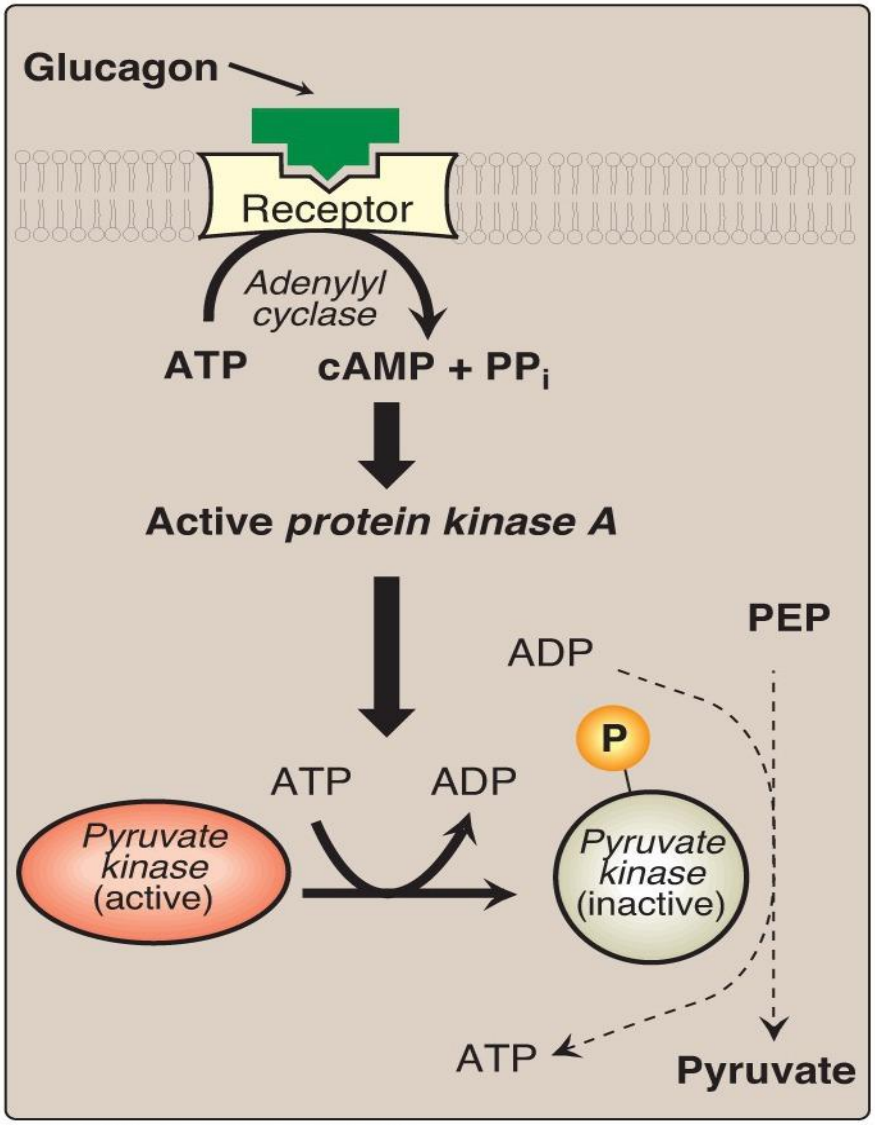
Phosphofructokinase 1 and this enzyme :

1)Activated by low energy molecules (AMP, F-2,6-bisP).

2)Inhibited by high energy molecules (ATP , citrate).

*لما يكون عندي طاقة ما في داعي اعمل glycolysis لهيك بعملوا تثبيط والعكس صحيح
اذا فيش طاقة بدي اعمل glycolysis .

Note : we have feedback inhibition of hexokinase or GK by glucose 6 phosphate molecule itself rather than the localization of the enzyme .



حتى ما نتخربط التنظيم بشكل عام بصير للخطوة الاولى والثالثة والاخيرة بالسلايدات قبل حكينا عن تنظيم الخطوة الاولى والثالثه اما هلا رح نحكي عن تنظيم الخطوة الاخيرة :

*in the last step we will convert the phosphoenol pyruvate (PEP) to pyruvate by pyruvate kinase .

This enzyme is going to be regulated by phosphorylation and dephosphorylation and it will be inactivated by phosphorylation .

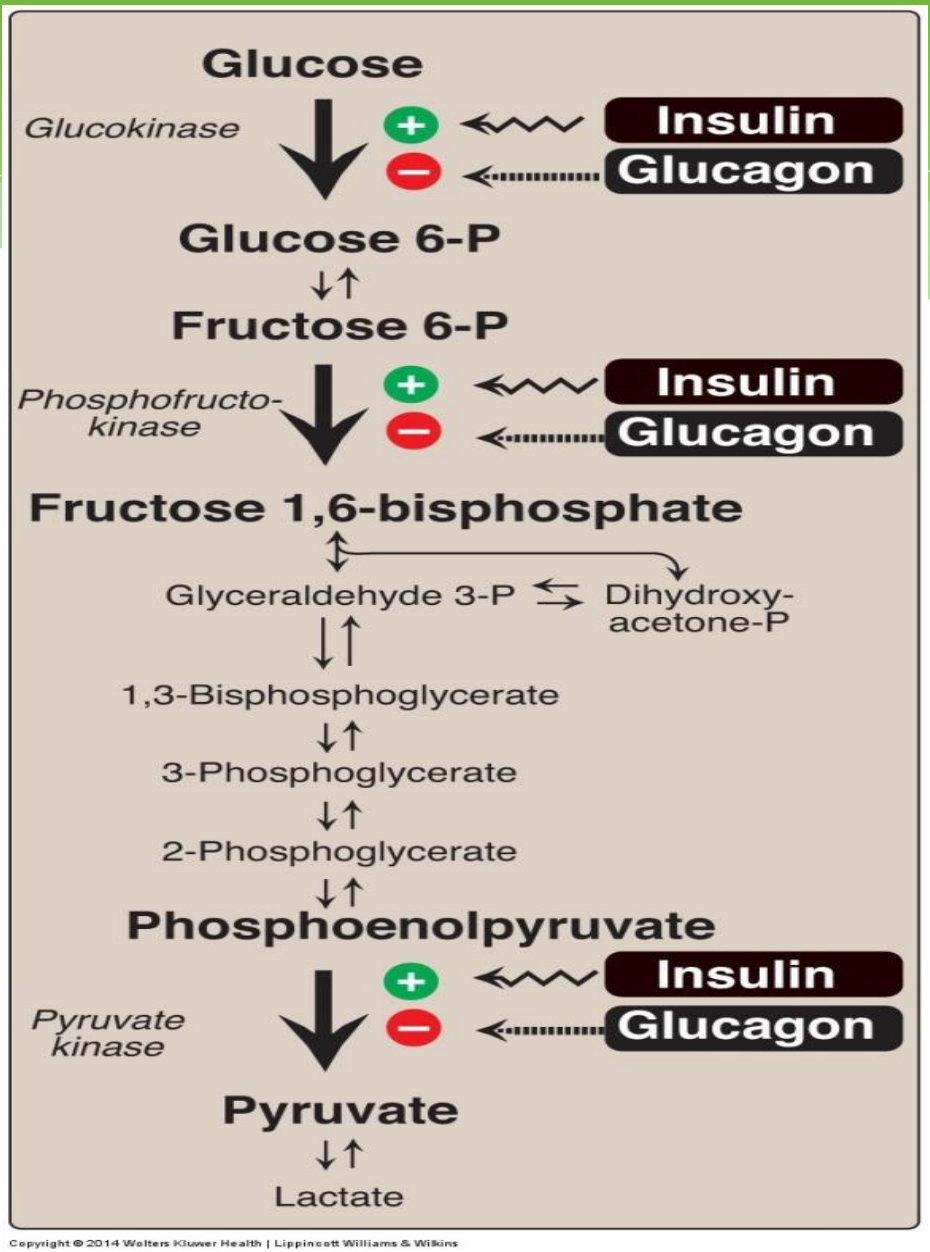
Glucagon hormone will activate signaling pathway that is responsible for the phosphorylation .

Note : glucagon represents the low glucose level (fasting state) and in this process there is no sense to complete the glycolysis process so it is logic to stop the glycolysis by phosphorylation by glucagon .

HORMONAL REGULATION OF GLYCOLYSIS

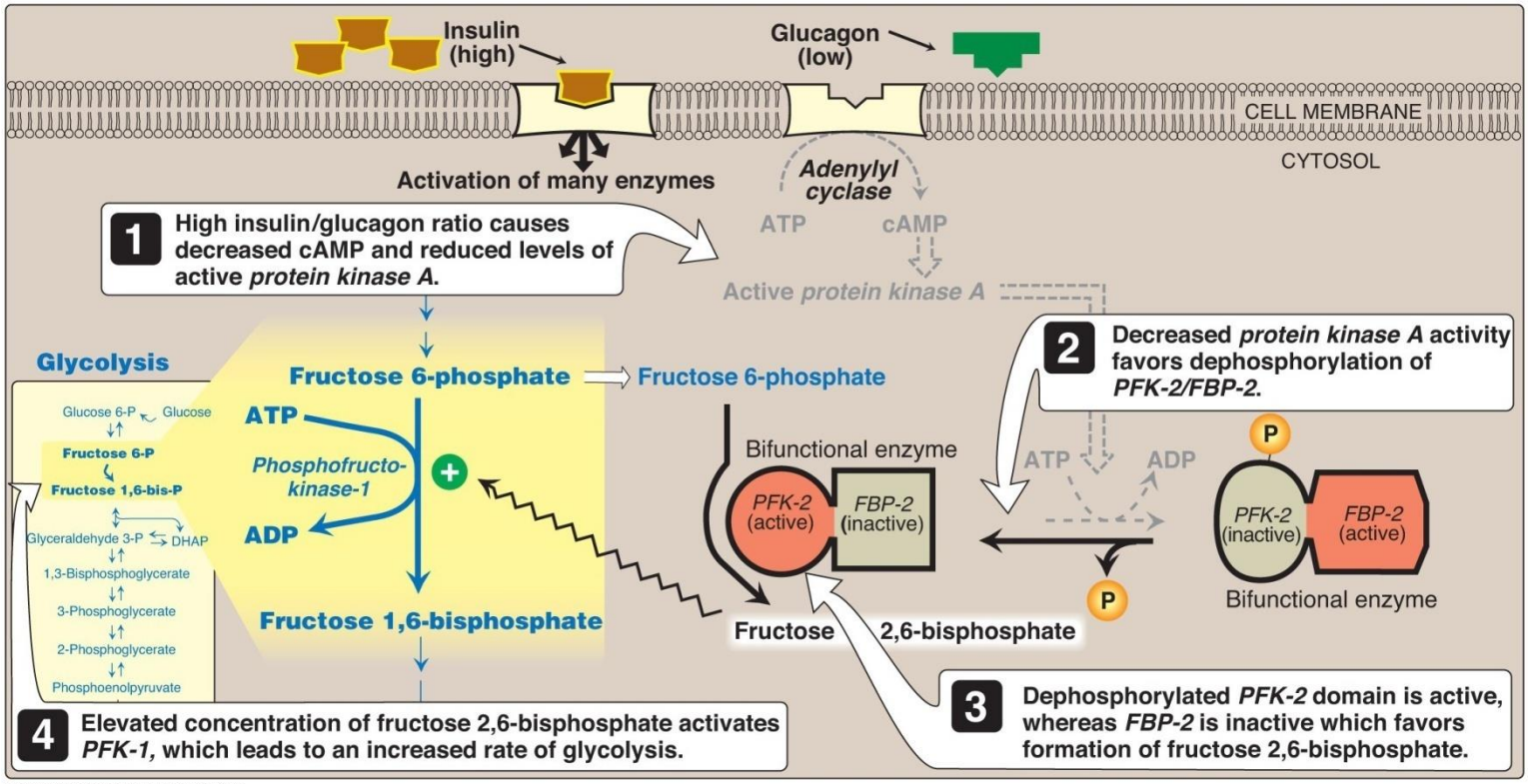
*insulin is responsible for the activation of first , third and last step , while glucagon is responsible for the inactivation or inhibition of the same steps .

Note : these steps are irreversible and controlling the glycolysis process



Regulation of GLYCOLYSIS

- **Figure 8.17**



* شرح السلايد السابق :

* We are going to regulate the phosphofructokinase 1 either by activation or deactivation :
* it is activated by similar enzymes called phosphofructokinase 2
* Generally we want to know the function of insulin and glucagon in the signal transduction in the liver ,they are activate phosphorylation (if there is glucagon)or dephosphorylation (if there is insulin), and both of them depend on the presence of glucose molecules .

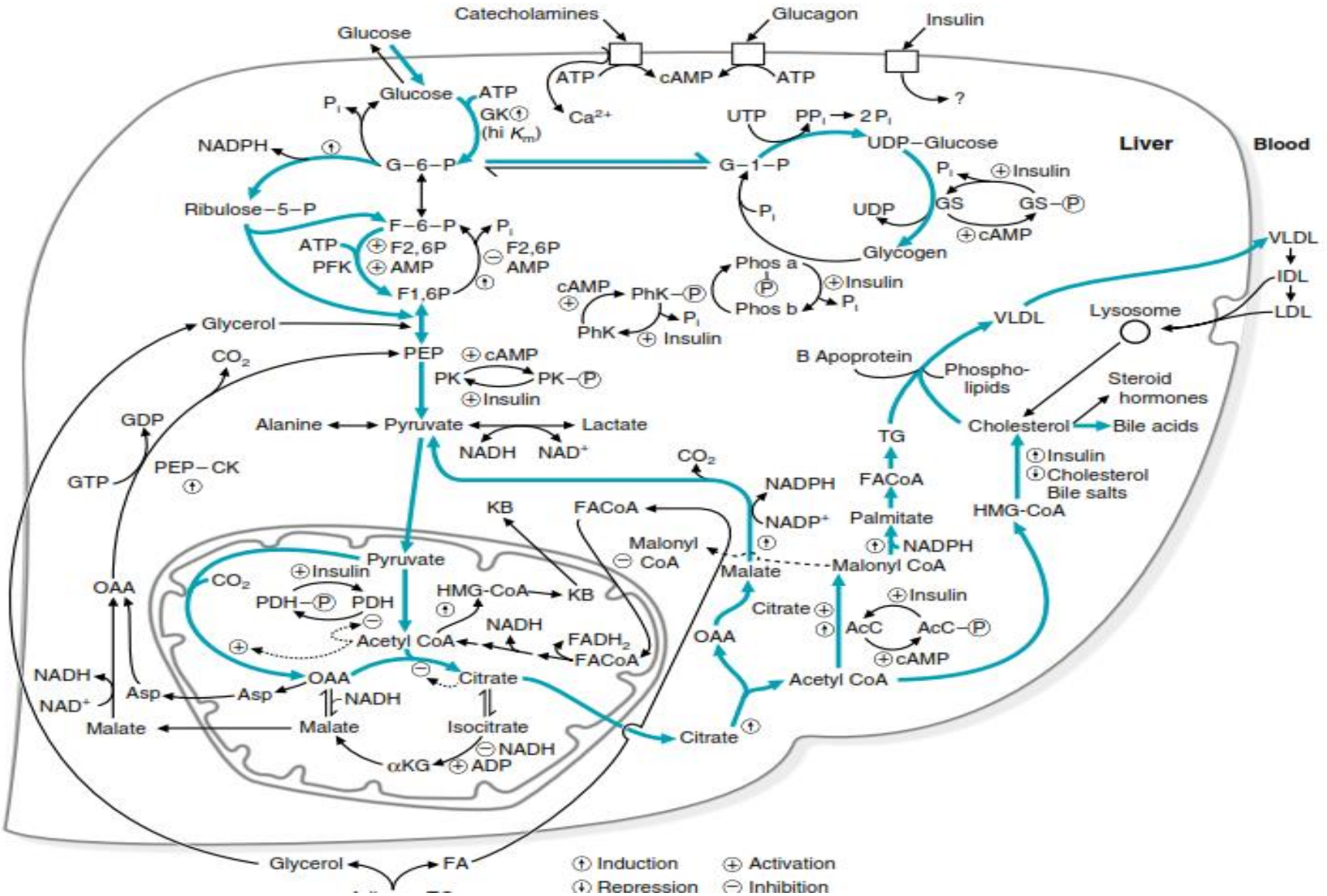
Table 36.2. Flowchart of Changes in Liver Metabolism

When blood sugar increases: Insulin is released, which leads to the *dephosphorylation* of:	When blood sugar decreases: Glucagon is released, which leads to the *phosphorylation* of:
• PFK-2 (now active)	• PFK-2 (now inactive)
• Pyruvate kinase (now active)	• Pyruvate kinase (now inactive)
• Glycogen synthase (now active)	• Glycogen synthase (now inactive)
• Phosphorylase kinase (now inactive)	• Phosphorylase kinase (now active)
• Glycogen phosphorylase (now inactive)	• Glycogen phosphorylase (now active)
• Pyruvate dehydrogenase (now active)	• Pyruvate dehydrogenase (now inactive)
• Acetyl CoA Carboxylase (now active)	• Acetyl CoA Carboxylase (now inactive)
Which leads to *active*	Which leads to *active*
• Glycolysis	• Glycogenolysis
• Fatty acid synthesis	• Fatty acid oxidation
• Glycogen synthesis	• Gluconeogenesis

Notes about the table :

*Phosphorylase kinase and glycogen phosphorylase now inactive because we don't want to break down the glycogen because we have glucose .

*acetyl CoA carboxylase is responsible for synthesis of fat .



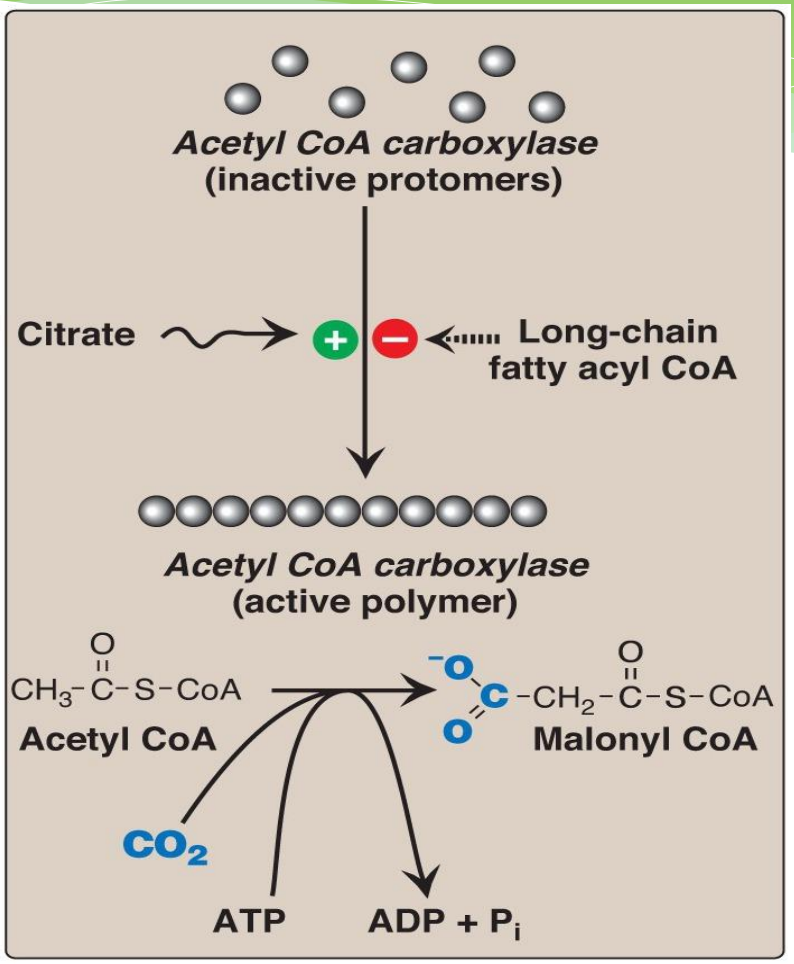
* بس بدنا من هاد السلايد نعرف انو الجسم بتعامل مع الكربوهيدرات ويحولها بالنهاية ل lipids

C. Lipid Metabolism

* Long-chain fatty acids are a major fuel for the liver during periods of fasting

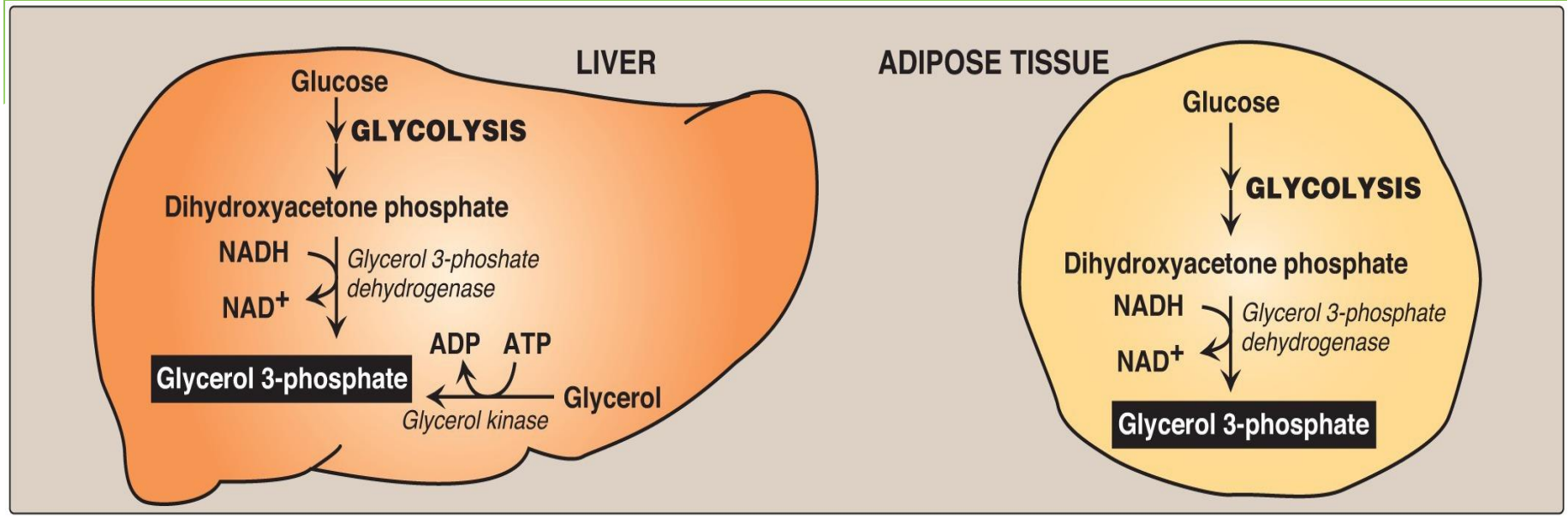
* PEROXISOMAL OXIDATION OF VERY-LONG-CHAIN FATTY ACIDS
* Similar to beta oxidation ,but it is the peroxisomal one which is some how different from it
* Note : beta oxidation for short and medium fatty acids ,while peroxisomal responsible for long chain F.A.

DE NOVO SYNTHESIS OF FATTY ACIDS



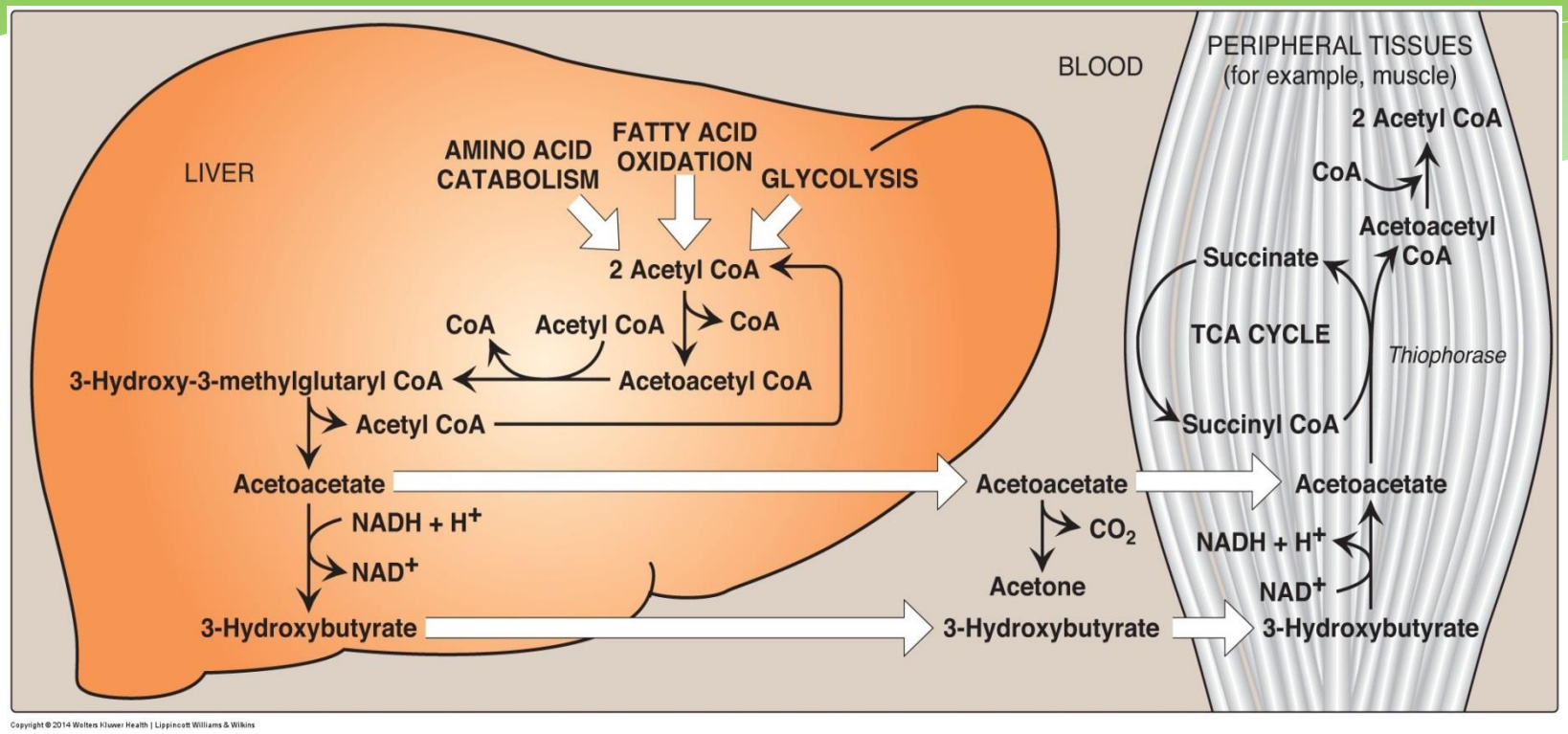
* *in general if we have well fed state we will synthesize F.A and eventually lipids and this process requires rate limiting enzyme during the fatty acid synthesize which is acetyl coa carboxylase enzyme which is responsible for the formation of malonyl coa from acetyl coa .
* *acetyl coa is very well known molecules that will be generated from either carbohydrate or from amino acids and eventually will be converted to malonyl coa and fatty acids .
* *so malonyl coa will be converted to F.A and these F.A if they are found in high concentration will inhibit the action of the enzyme by inhibiting the action of polymerization by acetyl coa carboxylase enzyme ,while citrate will activate that .
* *THE RESULT : we could convert the carbohydrate and amino acids to acetyl coa and then to FATS .
* Note : malonyl coa is the precursor for fat synthesis

DE NOVO SYNTHESIS OF FATTY ACIDS



*We need the fatty acids that are generated by fatty acid synthase(ما حكينا عن تفاصيله)
*the glycerol molecules are important to synthesis the TGA(we need to synthesis it fatty acids as well as the glycerol molecules in the active (glycerol3 phosphate)) .
*in liver : we have two sources responsible for formation of glycerol 3 phosphate ,one by glycerol 3 phosphate dehydrogenase enzyme and the other one is glycerol kinase which can deal with glycerol (naked glycerol if you would).
*in adipose tissue : we have one route for synthesis of glycerol 3 phosphate .
Note : fat is 3 fatty acids bind with glycerol 3 phosphate .

KETONE BODIES: AN ALTERNATE FUEL FOR CELLS (continued)



* *we do oxidation process for many molecules(carbohydrate ,fat , amino acids) including the fat ,and oxidation of these molecules generate what we called ketone bodies (acetoacetate , acetone(volatile molecule), 3-hydroxybutyrate),these molecules are generated in the liver when there is oxidation of fat specifically when we have starvation conditions or when we have diabetic conditions .
* And these ketone bodies will be transported to other tissues in order to supply them as a flue molecules specially the CNS and other types of cells that rely on ketone bodies .
* Note : liver itself can't metabolized ketone bodies by itself

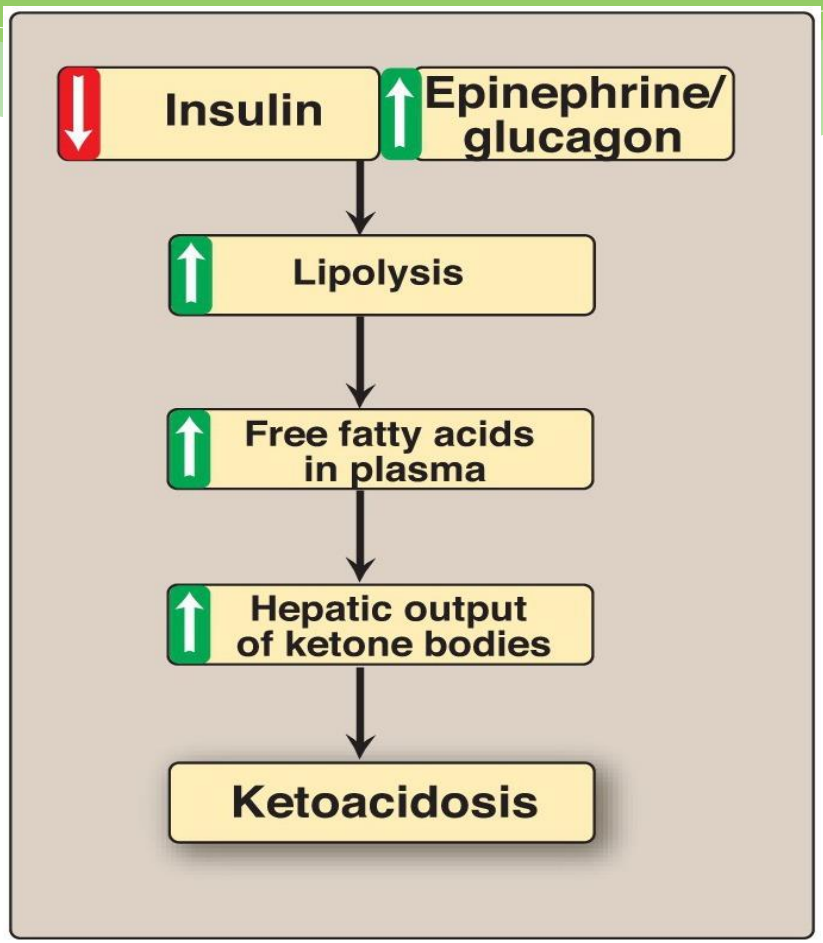
يعني ما بقدر يستخدمهم كمصدر للطاقة لانه الكبد فاقد لانزيم اسمه thiophorase

*so generally speeking ,most of the tissues can deal with ketone bodies because they can convert them back to acetoacetyl coa and then to acetyl coa in order to enter the kreb cycle because these cells have thiophorase enzyme which is responsible to convert of acetoacetate to acetoacetyl and this enzyme doesn't present in the liver .

KETONE BODIES: AN ALTERNATE FUEL FOR CELLS

*we have starvation condition so we don't have glucose so the insulin in lower concentration compared to glucagon and epinephrine and the situation will cause lipolysis so more fatty acids and it will be converted to acetyl coa and accumulation of acetyl coa will cause the generation of ketone bodies and eventually will cause ketoacidosis .

*مهم في حالة ال DM or starvation انو ننتبه لعملية ال ketoacidosis .



Amino Acids Metabolism

Study hard passion and remember that you will be a good doctor in the future ☺
I love you all ☺

Table 46.2. Nitrogen-Containing Products Produced by the Liver

Product	Precursors	Tissues	Function
Creatine	Arginine, glycine, and S-adenosyl methionine (SAM)	Liver	Forms creatine phosphate in muscle for energy storage. Excreted as creatinine.
Glutathione	Glutamate, cysteine, glycine	All tissues but highest use in the liver	Protection against free radical injury by reduction of hydrogen peroxide and lipid peroxides. In liver and kidney forms mercapturic acids.
Purines	Glycine, glutamine, aspartate, carbon dioxide, tetrahydrofolate, PRPP	Liver, small amounts in brain and cells of the immune system	Adenine and guanine nucleosides and nucleotides. DNA, RNA, and coenzymes, and energy-transferring nucleotides.
Pyrimidines	Aspratate, glutamine, carbon dioxide	Liver, small amounts in brain and cells of the immune system	Uracil, thymine and cytosine
Sialic acid (NANA), other amino sugars	Glutamine	Most cells	In the liver, synthesis of oligosaccharide chains on secreted proteins. Most cells, glycoproteins, proteoglycans, and glycolipids.
Sulfated compounds	Cysteine	Liver and kidney produce sulfate	Many cells use sulfate in blood for formation of PAPS, which transfers sulfate to proteoglycans, drugs, and xenobiotics
Taurine	Cysteine	Liver	Conjugated bile salts
Glycocholic acid, and glycocheno-Deoxycholic acid	Glycine, bile salts	Liver	Conjugated bile salts are excreted into the bile and assist in the absorption of lipids and fat-soluble vitamins through the formation of micelles
Sphingosine	Serine and palmitoyl CoA	Liver, brain, and other tissues	Precursor of sphingolipids found in myelin and other membranes
Heme	Glycine and succinyl CoA	Liver, bone marrow	Heme from liver is incorporated into cytochromes. Heme from bone marrow is incorporated into hemoglobin.
Glycine conjugates of xenobiotic compounds	Glycine, medium-size hydrophobic carboxylic acids	Liver, kidney	Inactivation and targeting toward urinary excretion
Niacin	Tryptophan, glutamine	Liver	NAD, NADP coenzymes for oxidation reactions
One-carbon methyl	Glycine, serine, histidine,	Most cells, but highest in liver	Choline, phosphatidylcholine, purine and

*الجدول بس بدنا نعرف منه انو عندنا مجموهة من الاحماض الامينية باول عامود والعامود الثاني بحكي عن ال precursor يلي بدنا نستخدمهم والعمود الثالث بقول انو الكبد هو المكان الاساسي لل metabolism in order to generate these molecules.

*حكا بده نعرف بس الاشياء الاساسية مثلا انو الاحماض الامينية رح تكون ال **creatine , glutathione , purine , pyrimidine** , taurine , sphingosine , **heme** ,and other molecules can be generated from the metabolism of amino acids

Note :

*purine and pyrimidine are nitrogen bases that we used them in nuclic acid synthesis (DNA,RNA) .

*taurine is going to be produced by cysteine in the liver

*heme is going to be produced by glycine and succinyl coa .

Table 46.3. A Partial List of Proteins Synthesized in the Liver

Type of Protein	Examples
Blood coagulation	Blood coagulation factors: fibrinogen, prothrombin, Factors V, VII, IX and X. Also α-2 macroglobulin.
Metal-binding proteins	Transferrin (iron), ceruloplasmin (copper), haptoglobin (heme), hemopexin (heme)
Lipid transport	Apoprotein B-100, apoprotein A-1
Protease inhibitor	α1-Antitrypsin

Other things that are synthesized by the liver is blood coagulation factors and certain transporter like transferrin for the iron and ceruloplasmin , haptoglobin and hemopexin and these are in general metal binding proteins because they contain metals like iron and copper .

Also lipid transporters

Note : alpha 1 antitrypsin is working as elastase inhibitors .

So these molecules synthesize in the liver and doing certain vital functions .

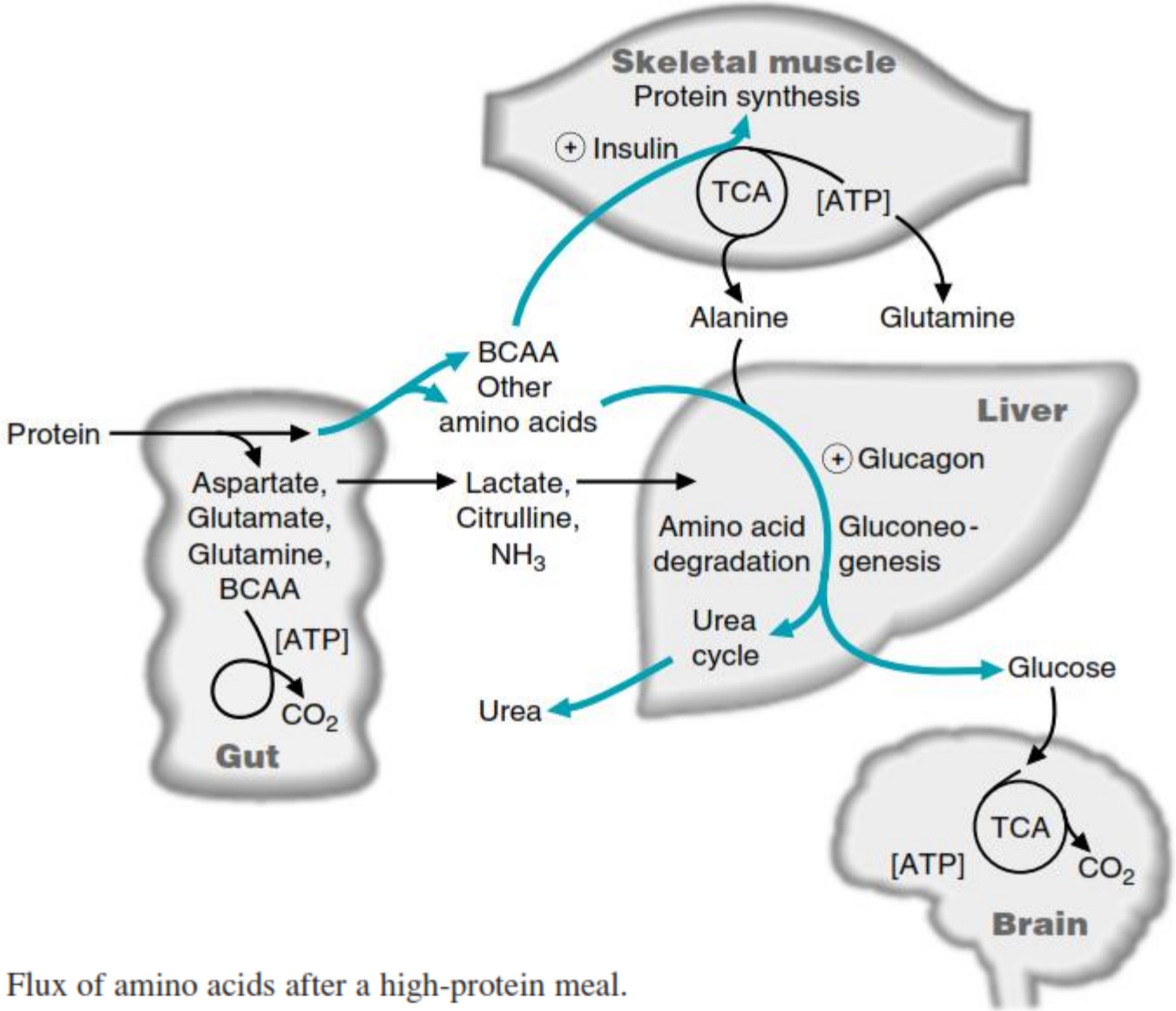


Fig. 42.15. Flux of amino acids after a high-protein meal.

شرح السلايد السابق :

*how the liver is going to metabolize the amino acids , actually the major source or the pool of amino acids are going to be metabolized by the liver includes either alanine which is generated from the metabolism of other amino acids or BCAA(brand chain amino acids) and other amino acids , all of these amino acids regardless to their source are going to be metabolized by the liver in order to produce glucose molecules and these amino acids are known as glucogenic amino acids .

*why the liver is interested to synthesize or to convert these molecules to glucose ? Because the liver is responsible for the supplying the body of glucose and that is why it is selective in choosing certain amino acids to produce glucose .

Then glucose molecules are going to metabolized again and assumed that it is going to be localized again by muscles cells and muscle cells will generate alanine again so we have a cycle of alanine glucose .

*الجلوكوز مو باللضرورة يروح على ال CNS بس من الاشياء المهمه هو ال CNS لهيك عندنا اشي اسمه glucose alanine cycle.

*the byproducts which is toxic products of these process is ammonia which is mandatory to be converted to urea as non toxic products

* So we don't prefer amino acids and proteins to produce energy because they generate nitrogen as ammonia so we convert it to urea.

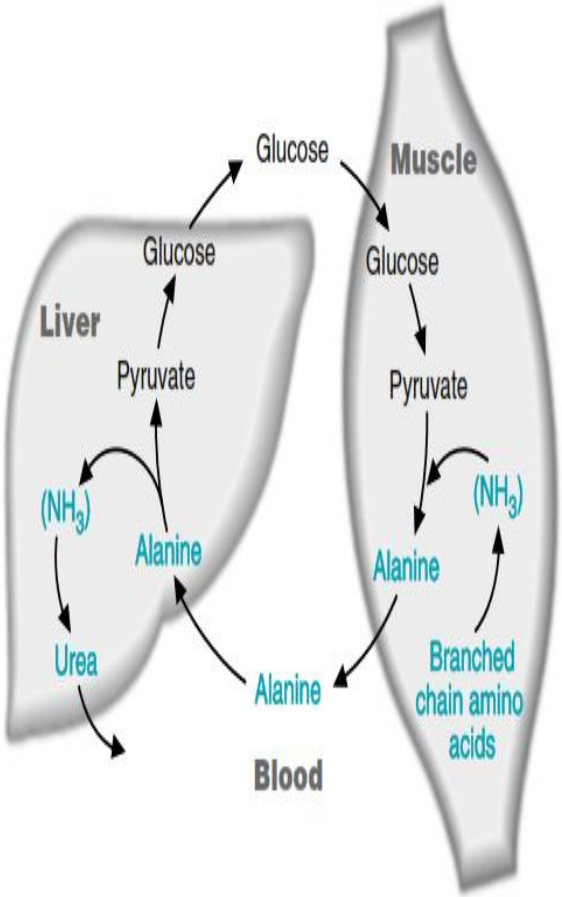


Fig. 42.12. Glucose-alanine cycle. The pathway for transfer of the amino groups from BCAA in skeletal muscle to urea in the liver is shown in blue.

* we have cycle of glucose which will be transported to peripheral tissues and after the metabolism of these tissue we will generate the alanine and amino acids that will be transported back to the liver and again will produce glucose so this is known as glucose alanine cycle .

Liver is the principle site of amino acid metabolism in humans.

1. The liver contains all the pathways for catabolism of all of the amino acids and can oxidize most of the carbon skeletons to carbon dioxide.

2. It contains the urea cycle.

3. After a mixed or high-protein meal, the gut uses dietary aspartate, glutamate, and glutamine as a fuel (during fasting the gut uses glutamine from the blood as a major fuel).

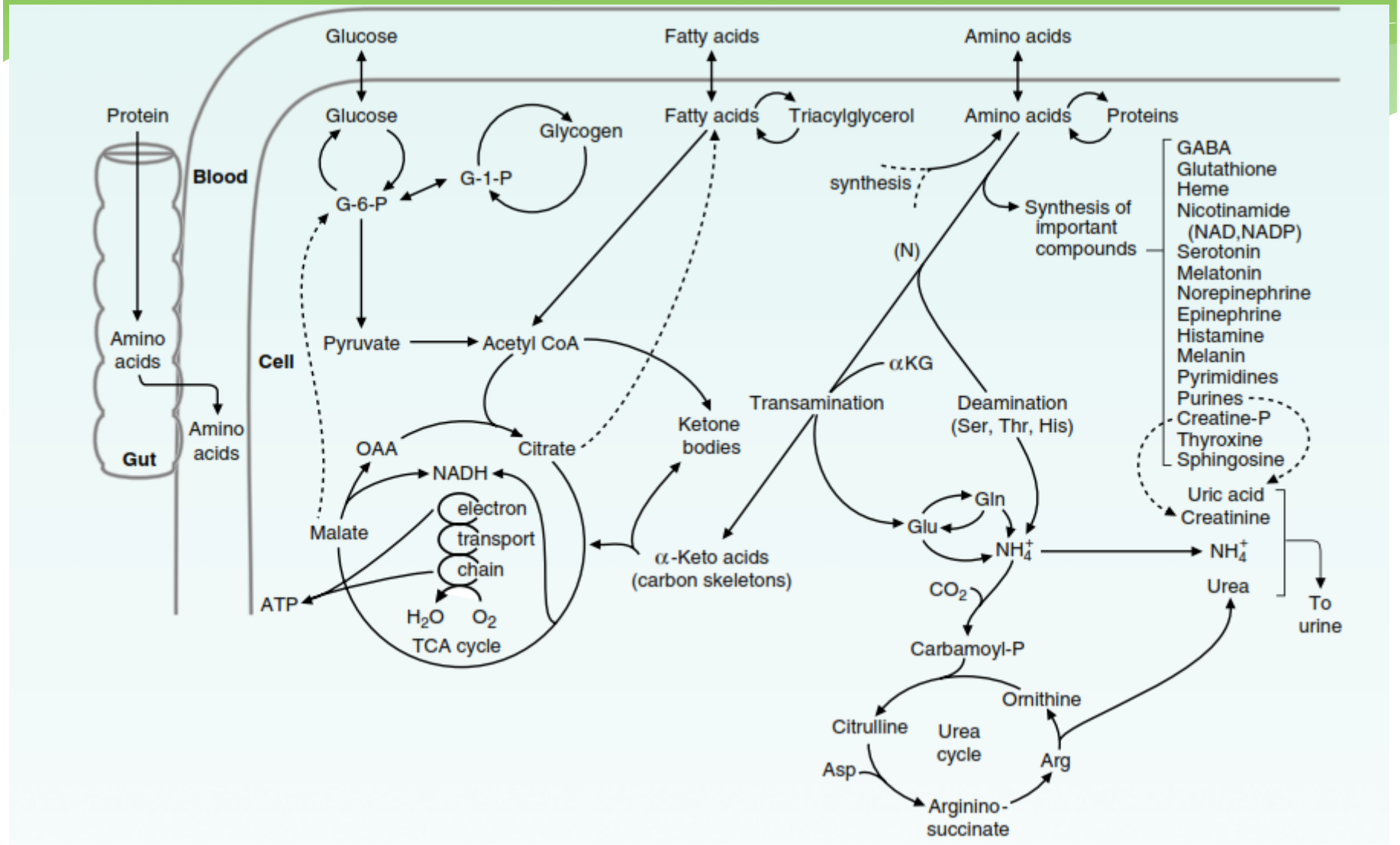
Liver is the principle site of amino acid metabolism in humans.

4. The branched-chain amino acids (valine, leucine, and isoleucine) can be used by most cell types as a fuel, including cells of the gut and skeletal muscle.

5. Most tissues transfer the amino acid nitrogen to the liver to dispose of as urea

6. The liver uses amino acids for the synthesis of proteins that it requires as well as for the synthesis of proteins to be used elsewhere.

Urea Cycle


Glucose
Fatty acids
Amino acids
Protein
Blood
Glucose
Glycogen
Fatty acids
Triacylglycerol
Amino acids
Proteins
G-1-P
G-6-P
synthesis
Synthesis of important compounds
(N)
GABA
Glutathione
Heme
Nicotinamide (NAD,NADP)
Serotonin
Melatonin
Norepinephrine
Epinephrine
Histamine
Melanin
Pyrimidines
Purines
Creatine-P
Thyroxine
Sphingosine
Amino acids
Cell
Pyruvate
Acetyl CoA
αKG
Transamination
Deamination (Ser, Thr, His)
Ketone bodies
Amino acids
Gut
OAA
Citrate
NADH
Gln
Uric acid
Creatinine
electron transport chain
Malate
Glu
NH_4^+
NH_4^+
α-Keto acids (carbon skeletons)
CO_2
Urea
To urine
ATP
H_2O
O_2
TCA cycle
Carbamoyl-P
Ornithine
Citrulline
Urea cycle
Asp
Arg
Arginino-succinate

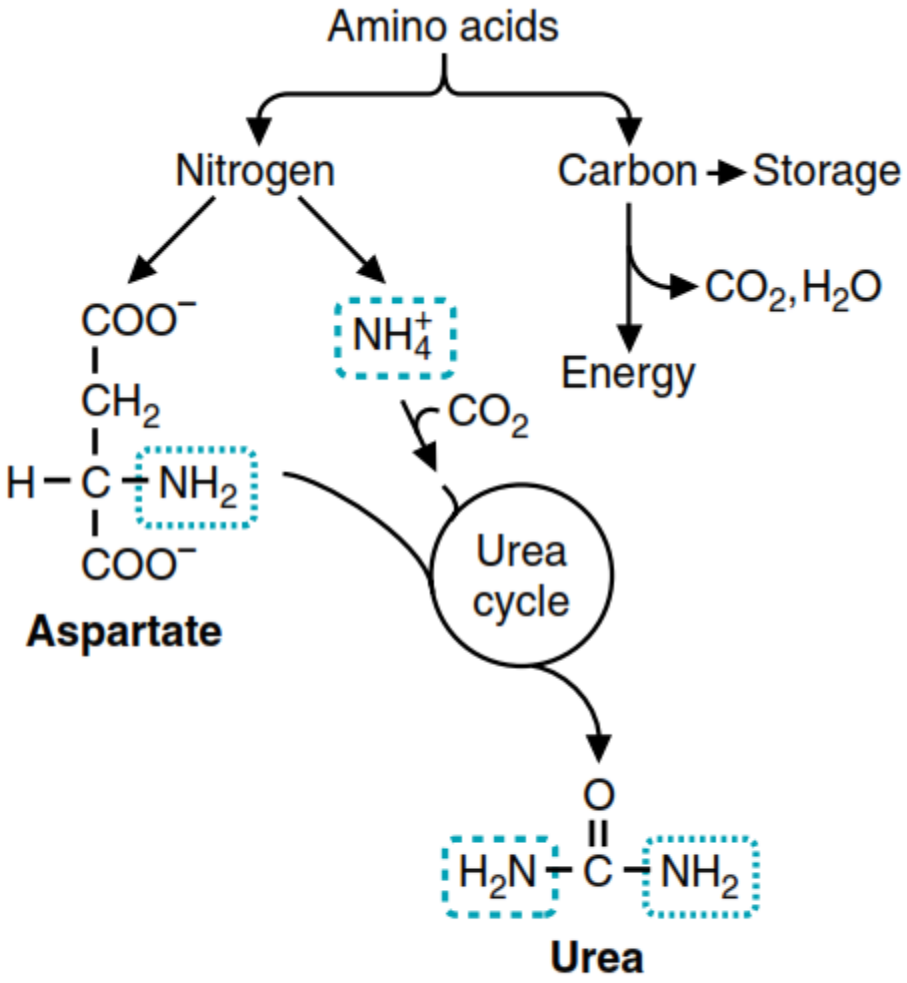


Fig 38.1. Fate of amino acid carbons and nitrogen. Amino acid carbon can be used either

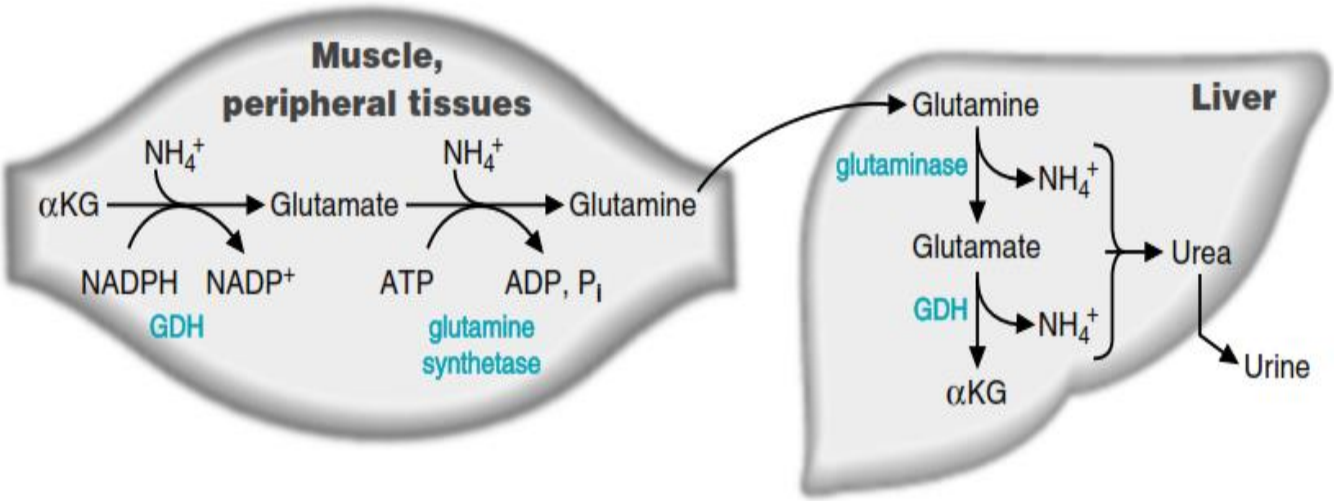


Fig. 38.11. Synthesis of glutamine in peripheral tissues and its transport to the liver. Within the liver, glutaminase converts glutamine to glutamate. Note how α-ketoglutarate can accept two molecules of ammonia to form glutamine. GDH = glutamate dehydrogenase.

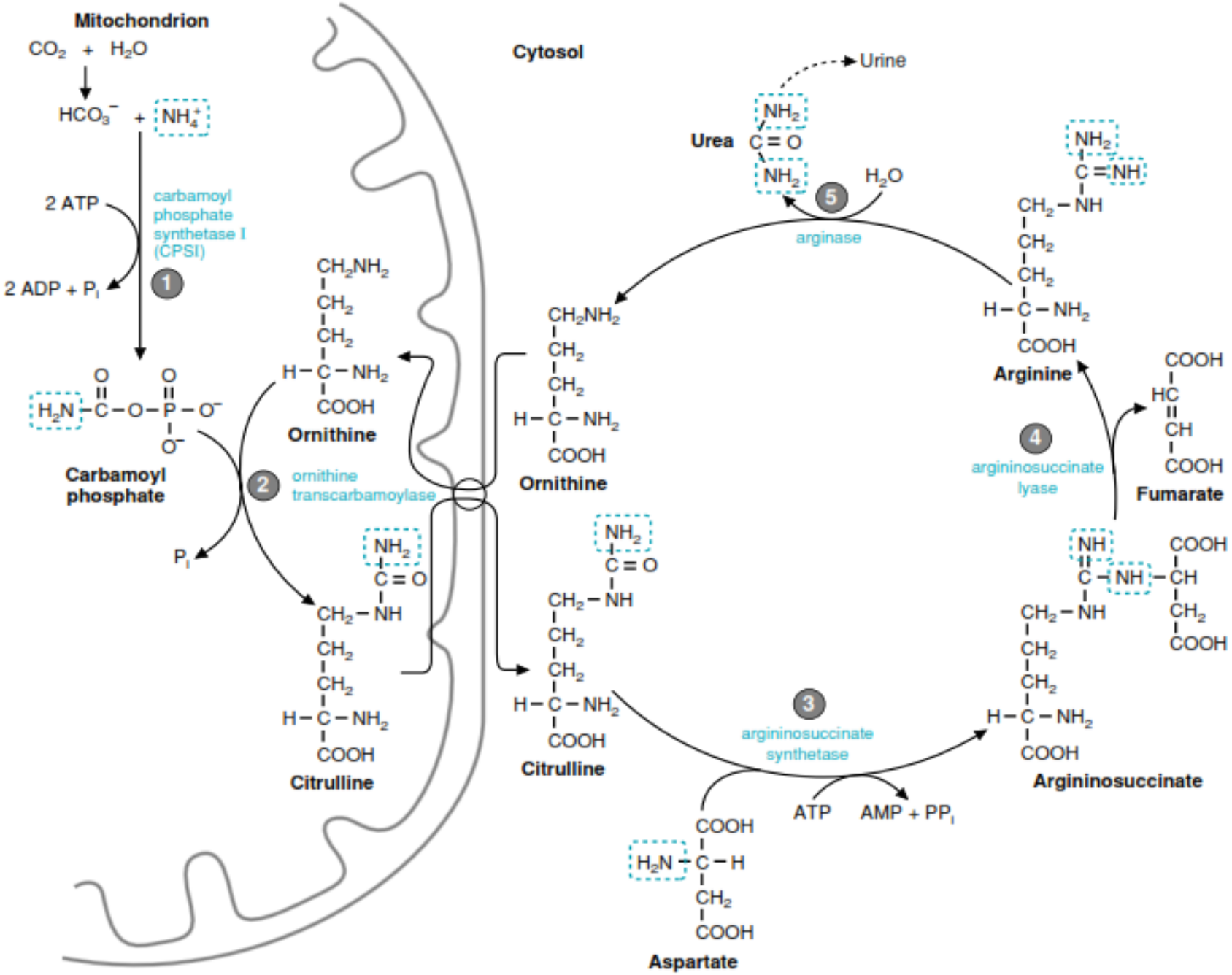


Fig. 38.12. Urea cycle. The steps of the cycle are numbered 1 to 5.

*شرح السلايد السابق :

Urea cycle :

*the urea cycle is localized in two locations (cytosol as well as the mitochondria because we need certain enzymes that are localized in the mitochondria and some other enzymes that are localized in the cytosol).

*in the mitochondria we start the urea cycle by the conjugation of co2 with h2o to generate carbonic acids or bicarbonic molecules in this case and it will be converted to carbamoyl phosphate and this is catalyzed by carbamoyl phosphate synthetase 1 **(this process two ATP molecules we use them to calculate the energy consumption that we will use in urea cycle)**

*ملاحظة 1: الخطوة الاولى تبعت تكوين ال carbamoyl phosphate استفدت منها انها خلصتني من احد جزيئات الامونيا

*ملاحظة 2 : عندي انزيم ثاني اسمه carbamoyl phosphate synthetase 2 ولكن هذا ما اله دخل بال urea cycle .

*then the carbamoyl phosphate is going to conjugate the ornithine which is another amino acids to form citrulline (الانزيم تبع هاي الخطوة مش مهم)

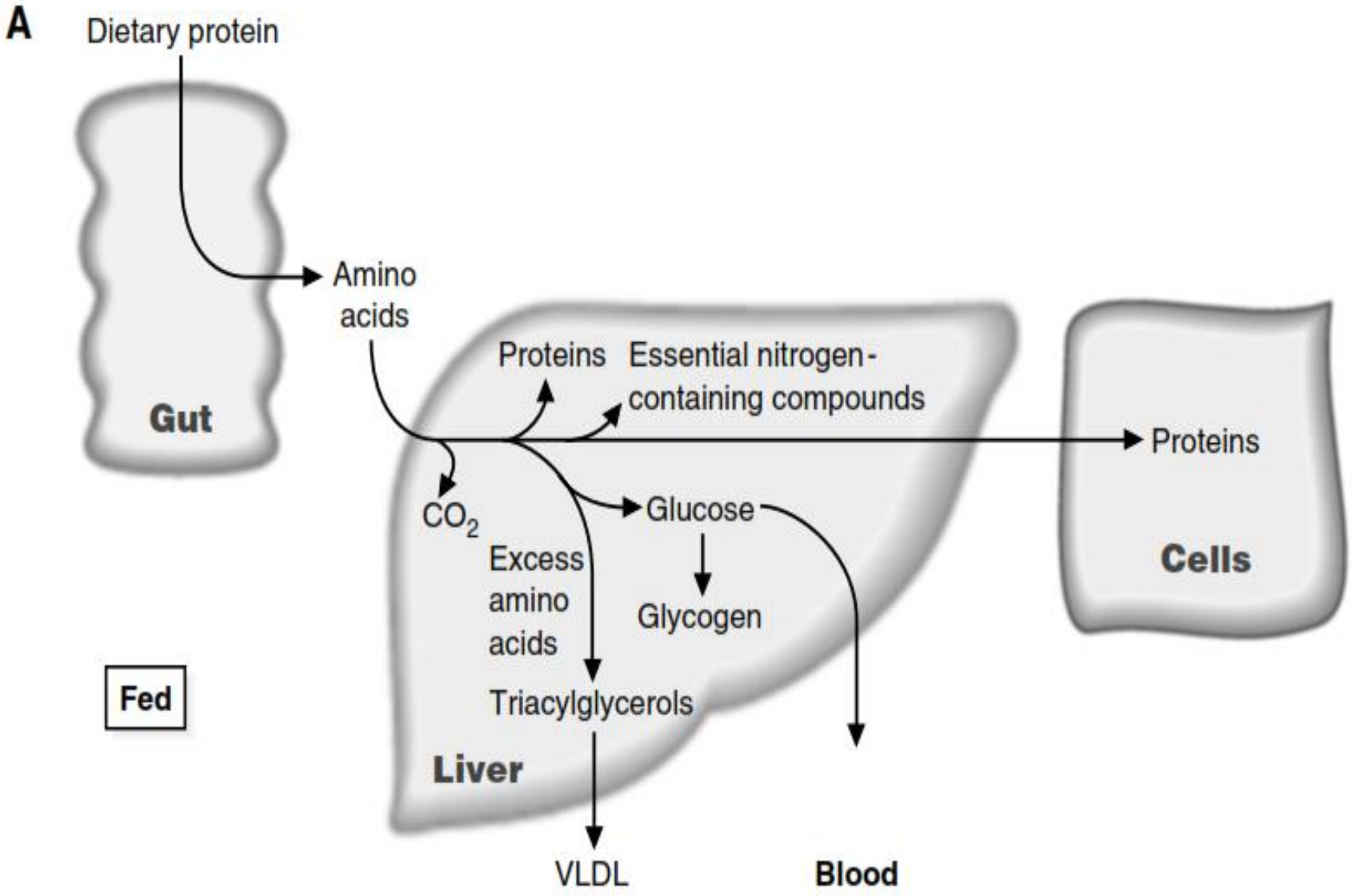
*the citruline is going to transported to cytosol and converted to argininosuccinate by conjugation of aspartate

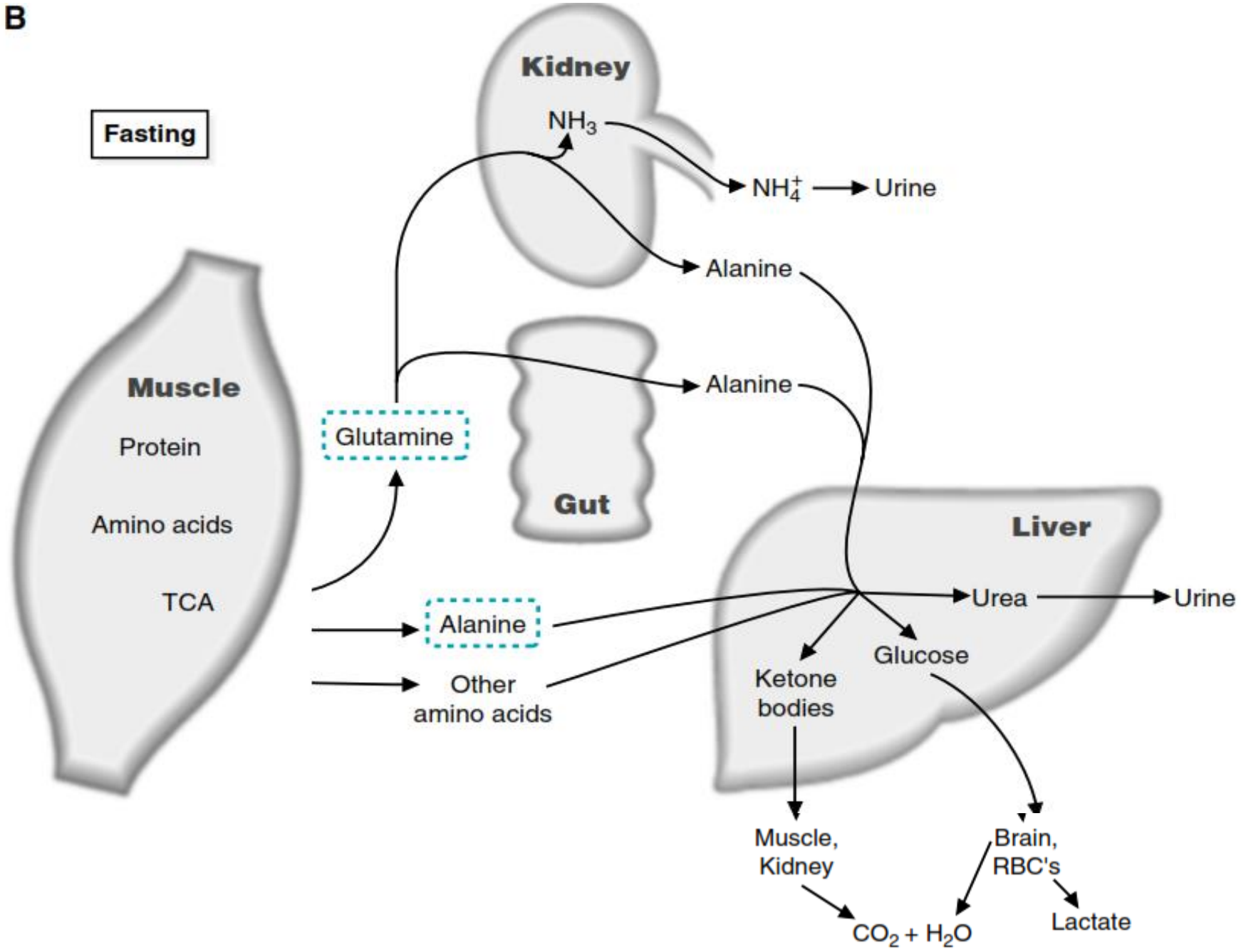
- The argininosuccinate has two ammonia molecules ,one from the citrulline and the second from aspartate

*by lyase enzyme this molecules will be converted to fumarate and arginine which contain the two ammonia molecules

*and arginase enzyme (مهم) will convert the arginine to ornithine by releasing two ammonia molecules with the carbon that is previously conjugated with the ammonia as a urea and the urea will be transported to urine and excreted outside the body as well as certain amount of ammonia

*بضل مجموعة من الامونيا بتطلع على شكل امونيا مش يوريا


A
Dietary protein
Amino acids
Gut
Proteins
Essential nitrogen-containing compounds
Proteins
CO_2
Glucose
Excess amino acids
Glycogen
Cells
Fed
Triacylglycerols
Liver
VLDL
Blood


B
Fasting
Kidney
NH_3
NH_4^+
Urine
Alanine
Muscle
Protein
Amino acids
TCA
Glutamine
Alanine
Gut
Liver
Urea
Urine
Alanine
Other
amino acids
Ketone
bodies
Glucose
Muscle,
Kidney
Brain,
RBC's
$CO_2 + H_2O$
Lactate