YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 1 - Biochemistry

Lec. Title : Special aspects of renal metabolism . Role of kidney in acid base balance

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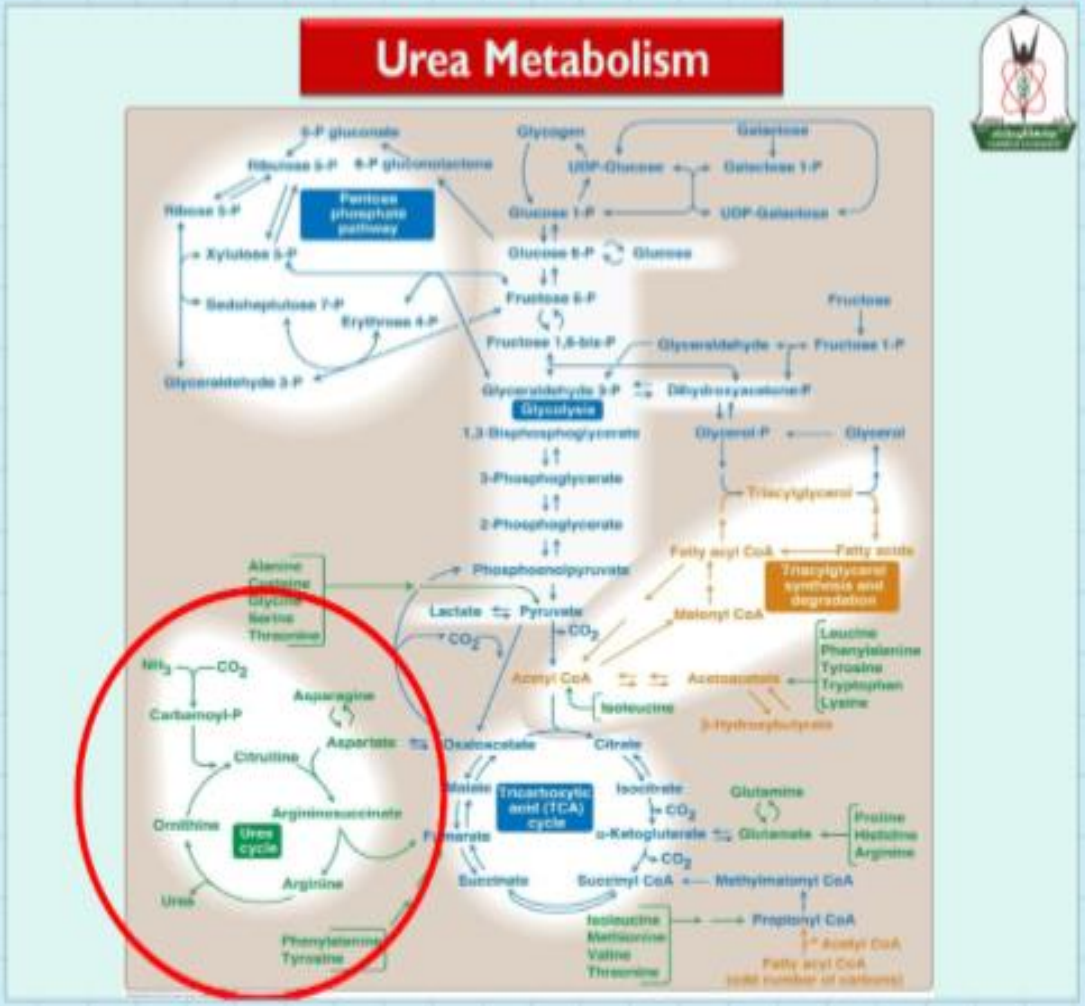
Special aspects of renal metabolism.
Role of kidney in acid base balance



*urea cycle is one of the pathaways that has kind of integration with the general pathaways that we already knew(glycolysis and kreps cycle)

*urea cycle is responsible for the production of urea (that is why it is called urea cycle), and it has certain metabolites that integrated with kreps cycle like *formation of fumarate
or *consumption of aspartate which can be converted as well to oxaloacetat.

the small conection between urea and kreps cycle

*precursor that is responsible for formation of urea starting with the amonia molecule plus the carbon dioxide .

* urea cycle starts in the mitocondria because the enzymes that are responsible for the conjugation of carbon dioxide and amonia are localized thier (mitocondria)

*the first molecule that will be formed is the (carbamoyl-p) then it will coneverted to citrulline (type of amino acids) that will be conjugated with aspartate to form what is called argininosuccinate and lyase enzyme it will be converted into fumarate and arginine
* the arginine will be cleaved to form urea and ornithine. and then it will be converted back into citrulline in the mitochondria .

*the rest of the cycle which is starting from citrulline until the formation of urea that occur in the cytosole.

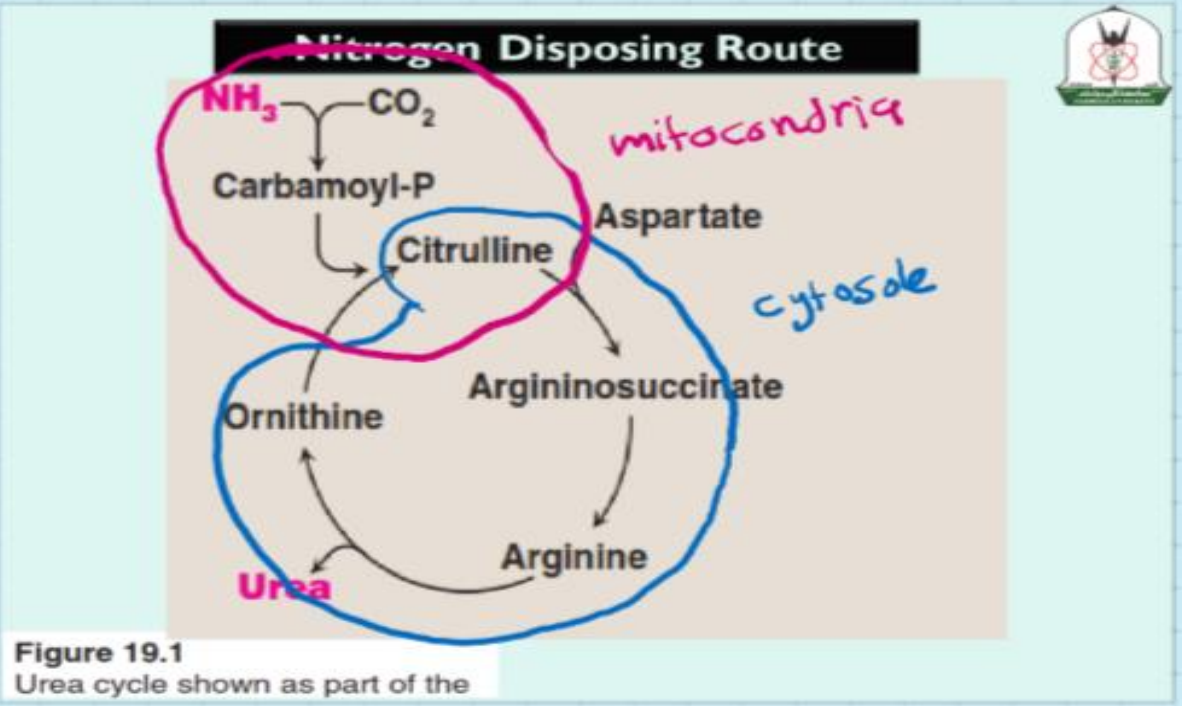
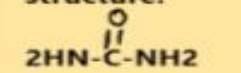


Figure 19.1
Urea cycle shown as part of the

urea its self consists of the following structure:



UREA consists of one amonia molecule that come from the free amonia and the carbon dioxide (the carbonyl group of the urea)and other amonia that came from aspartate (it presents another source of amonia)

UREA CYCLE IS OCCURING IN:

ORGAN: in the liver → ORGANELLs: start in the mitocondria then to cytosole

the major thing for the urea cycle and the major duty is to detoxify the amonia by formation of the urea, that is why we have urea cycle because we have to convert this toxic molecule (the amonia) to non toxic one (urea) , which can be easily excreted from body by the renal system .

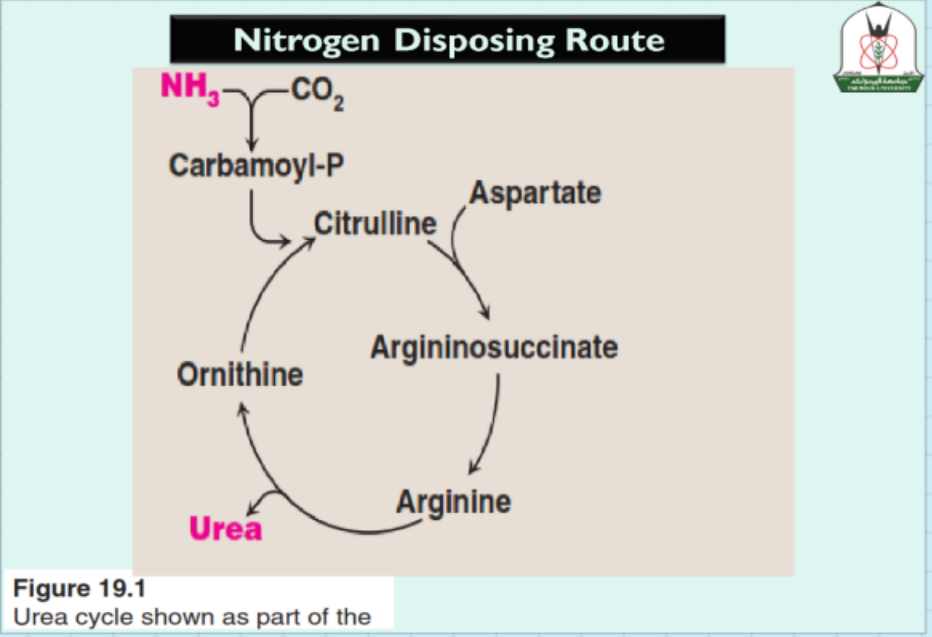


Figure 19.1
Urea cycle shown as part of the

disposing of nitrogen which is the toxic component of the amino acids metabolism or nitrogen containing compound that we have in our body.
*the amonia is the toxic because it is involved in the reversing of the what is called deamination process and it is toxic to the nervous system

nitrogen toxicty it is the reason of the amino acids are not usually used as a source of energy

organic molecules such as carbohydrate as well as lipids they can be used as source of energy , because they are hydrocarbons ,consists of(carbon,hydrogen and oxygen).

* amino acids they are an organic molecules but they have amin group
(*مصدر غير مفضل للطاقة)
_amino acids can be used , but they are not the major source of the energy in the body.

*presence of the amonia as a waste and it is toxic.

---

urea cycle starts with carbon dioxide and amonia and it will form carbamoyl-p then form citrulline in the mitochondria ,then citrulline will be transported into the cytosole and it will be conjugated with aspartate to form argininosuccinate and it will be cleaved to form fumarate which integrated with kreps cycle
and arginine it will be continued with urea cycle

مراجعة للurea cycle:

(the arginase will cleave the arginie) حتى تطلع اليوريا

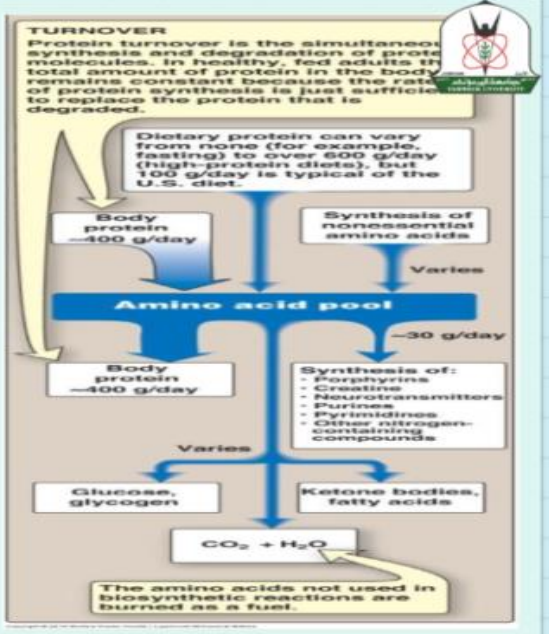
then form the ornithine which it will transported back into the mitochondria and then it will start onther cycle

*so ornithin is conjugated with carbamoyl-p to form citurlline
ornithin , citurlline they are amino acids because they are formed from arginine

Protein are different from CHO and Lipids by having NO storage form as a supply for amino acids for future need

Therefore, any excess amino acids will be degraded to produce free ammonia and α-keto acids **BY**

Transamination and Oxidative deamination



amonia come from (nitroge containing compaounds) ,amino acids in the body usually in serum or blood they come from differents sources :

the daily intake protein (dietry protein

protein turnover (recycling of protein in the body

synthesis of nonessintial amino acids

***10 aminoacids that can be synthesis in the body**

amino acids can be used in different metabolic pathways:

1

body protein : constant turnover of protein (degradation of body proteins,from destroying cells)

the protein they will be formed again.

2

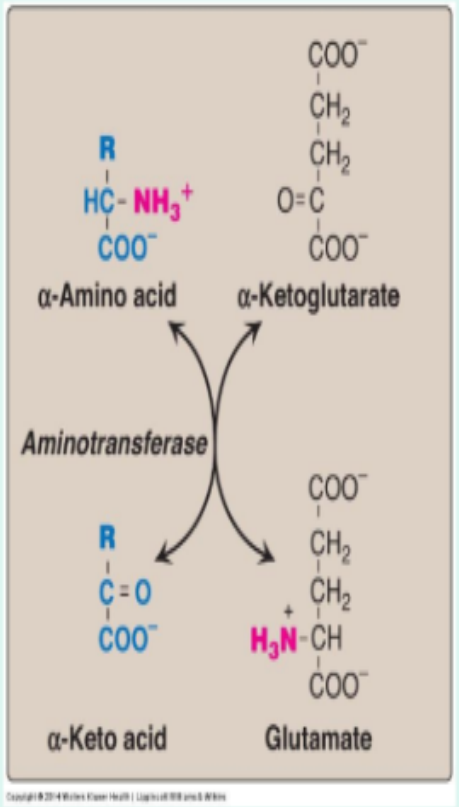
other amino acids will be used to synthesis special molecules like prophyrine, creatine .....ect.

these compound are called nitrogen containing compound

3

some amino acids they can be used to synthesis glucose(glucogenic)or ketone bodies (ketogenic) or both

during the catabollism you will have these products (CO2 ,H2O)
*NITROGEN components they will be used to generate such molecules



the most important reaction that responsible for formation of free amonia is the transamination and oxidation deamination)

*these reaction are responsible for the production of the free amonia and the rest of amino acid is called keto-acid

in the transamination process which catalyse by aminotransferase enzyme (transaminas enzyme) is the responsible for the transfer of certain amin group from certain amino acid and we have always another half of the reaction, that converts the alpha- ketoglutarate to glutamate. <<<coupled reaction

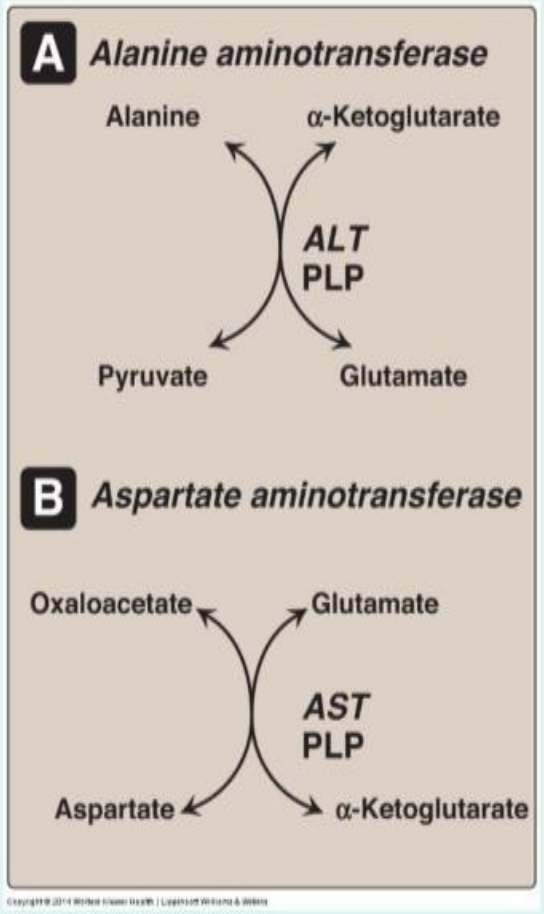
alpha-ketoglutarate is always parallel reaction or half reaction of this coupled reaction that will convered to glutamate

* and ver versus the glutamate coverted to alpha-ketoglutarate

this half of reaction is always present in transamination reaction

REASON:

they transfer the amin group in the amino acid to the alpha-ketoglutarate then it will converted to glutamate.



ALANINE as amino acid
alpha-ketoglutarate
* catalayzed by alanine transferase (ALT)and required a co-enzyme pyridoxal phosphate(PLP)

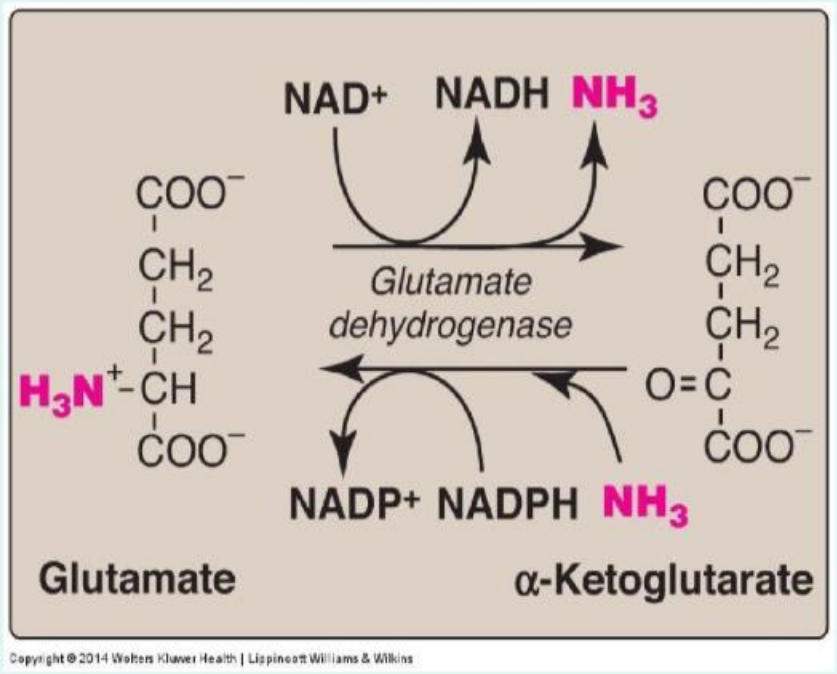
*alanine will be converted to pyruvate which is a ketoacid and the alpha-ketoglutarate will br converted to glutamate.

conversion of alpha-ketoglutarate to glutamate
and aspartate will be conerted to oxaloacetate,
and the oxaloacetate can be coverted to
aspartate.

*catalyzed by aspartate transferase (AST) and required pyridoxal phosphate(PLP)

Glutamate,Alanine and ,aspartate are nonessintial amino acids , they can be synthesis in the body

oxidative deamination



transamination of different amino acid forms glutamate, this glutamate will be converted to alpha-ketoglutarate without transamination reaction

oxidative : the NAD is involved in this reaction,
*NAD+TO NADH
*NADP+ TO NADPH

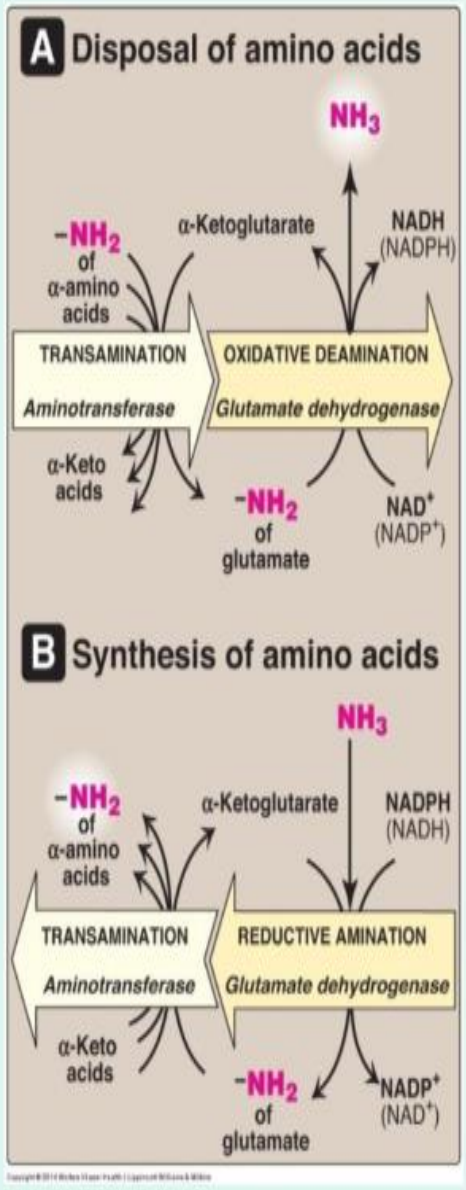
DEAMINATION ;
remove amine group in the glutamate as free amonia

*the enzyme that is involved in this reaction is the glutamate dehydrogenase;
dehydrogenase(in this reaction there is oxidation reduction process)

if you have extra amonia in the body so this amonia due to certain reasons (deficiency in the urea cycle or high toxicty of amonia) the amonia will push back the reaction to consume the NADPH and NADH.

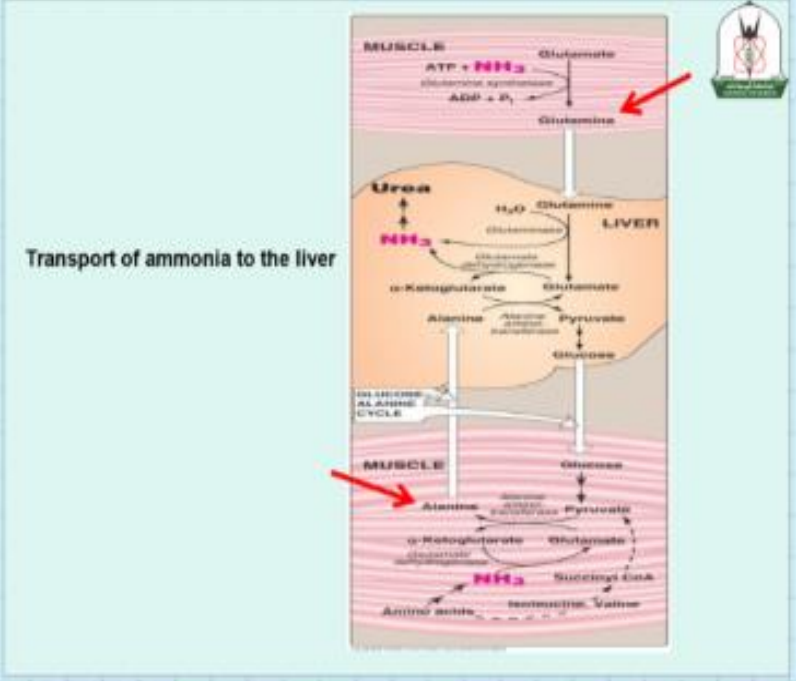
Amonia as the toxic molecule in the body they propose this mechanism as the toxic mechanism of the amonia it will be conasume the NADPH it help

NADPH is important because it help in anabolism it is reducing agent,



you have amino acid that are goning through the transamination reaction and the alpha-ketoglutarate will be converted to glutamate and the glutamate will be involved in the oxidation deamination and producing high amonia

* if you have high concetration of amonia it push back the reaction in order to consume the NADPH OR (NADH)



Transport of ammonia to the liver

the body is desposing the nitrogen that we have in amonia by the formation of glutamin , by glutamin synthase

* glutamin molecule is responsible for the transportiation of the amonia in the body from cells to the liver

this reaction required ATP (consumption) in order to conjugated free amonia to form glutamine , this will be transported to the liver

once it reach the liver the glutaminase responsible for the deamination , and it is completely dufferent from the glutamate deamination

it is one of the important mechanism to transport amonia from peripheral tissues to the liver, so the amonia will be used to form the urea which is less toxic molcule

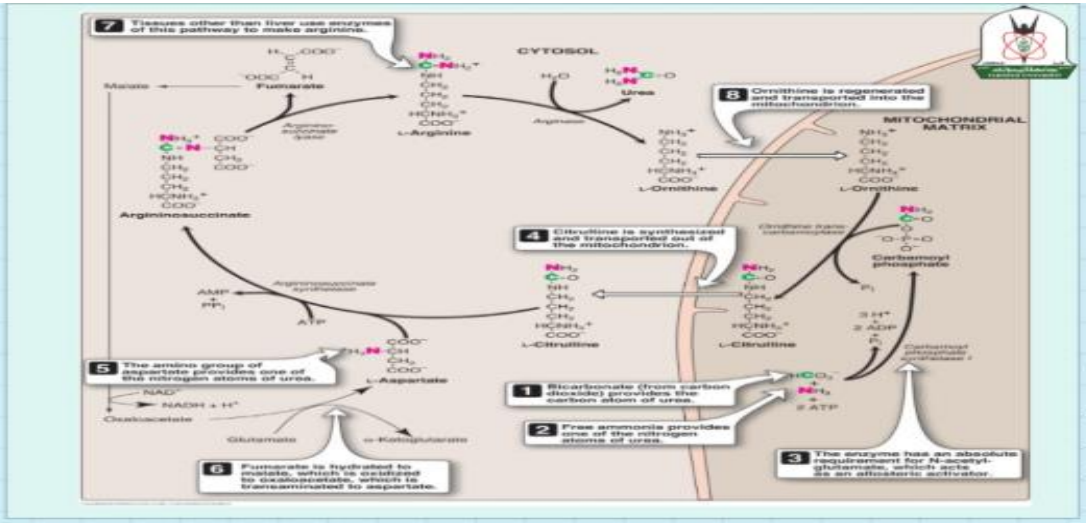
this mechanism

found in the kidney in order to release free amonia by glutaminase reaction

glucose-alanine cycle; which is responsible for the transportation of glucose from the liver (supplying body by glucose) through different mechanisms such as breaking of glycogen and gluconeogenesis; which is the formation of glucose from certain precurser in this case they are amino acids which are conevrted to (pyruvate) then can be converted to glucose.

the glucose can be transported by the circulatory system to th peripheral tissues and then it will be be used to form the pyruvate which is the end of glycolysis

* the pyruvate by transamination reaction in the peripheral tissues can be converted to alanine and the alanine will be transported back into liver in order to participate in the transamination reacrion, that will generate pyruvate again



urea cycle starts in the mitochondria by the formation of the carbamoyl-phosphate which is generated by conjugation of carbon dioxide and amonia +2ATP.

CO2 in this reaction is formed from bicarbonate

amonia that is generated by transamination and then oxidative deamination

2 ATP molecules that are important to form carbamoyl-phosphate

CO2 found in three forms in the blood

* t is dissolved directly in the blood
*bound to plasma hemoglobin
*converted into bicarbonate. The majority of carbon dioxide is transported as part of the bicarbonate system. (bicarbonate is part of buffer system)

carbamoyl-p= amonia +carbondioxide + one phosphate group that is come from atp molecules ⟶ it will generate 2ADP

the enzyme that is responsible for this reaction is called caramoyl-phosphate suynthase 1 , because there is carbomoyl-phosphate 2 in other reaction is not in the urea cycle

*carbamoyl-p is goning to be conjugated with ornithine which is localized in the mitochondria matrix in order to to form citrulline

*ornithine which is an amino acid that is converted to another amino acid (citrulline); because it can be transported outside , while the carbamoyl phosphate it self can not transported outside the mitochondria.

this reaction is required ornithine transcarbamoylase enzyme

*specific transporter for citrulline that will be transported into the cytosol and then it will be converted to argininosuccinate by conjugation of aspartate, which is came from oxaloacetate

this reaction is required argininosuccinate synthatase enzyme ⟶ (Synthetase enzyme there is involvement of ATP)

in this reaction we have one ATP molecule that is required for the activation of this reaction by converting the ATP to AMP

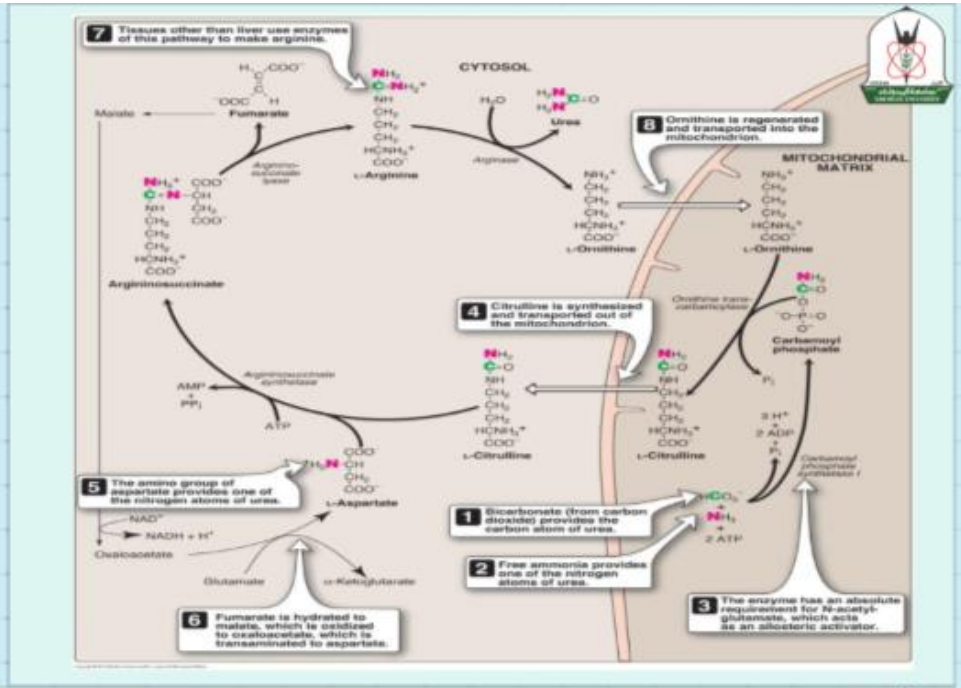
UREA CYCLE = من ناحية عدد ال ATP

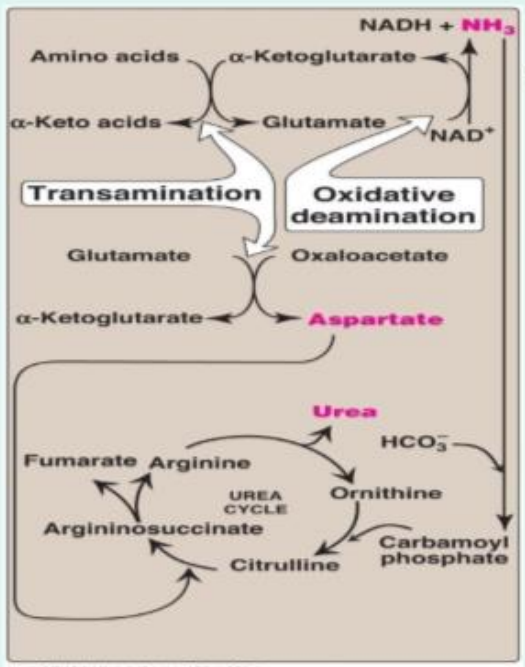
3ATP molecules

4 ATP molecules = ATP Equivalents

ΔG=7.35 ATP ⟶ ADP

ΔG=2*(7.35) ATP ⟶ AMP





argininosuccinate is a large molecule that came from conjugation of two amino acids (aspartate and citrulline)

* and by lyase enzyme (argininosuccinate lyase enzyme) you generate arginie as well as fumarate (it will be poart of the kreps cycle)

the arginine is going to be cleaved by arginase to releas urea(amonia)

*and ornithine which is transported back to the mitochondria

the pink color refer to the amonia to know the source of the amonia for the urea that will be formed in the future

co2 that come from of bicarbonate as well as amonia that come from aspartate and one as free amonia

Hyperammonemia

Serum ammonia are normally low (5–35 µmol/L)

Ammonia has a direct neurotoxic effect on the CNS

At high concentrations, ammonia can cause coma and death

1. **Acquired hyperammonemia:**

2. **Congenital hyperammonemia:**

    1. 1:25,000
    2. Ornithine transcarbamoylase deficiency, which is X-linked

hyperammonemia is high concetration of amonia in the blood ,emia refers to the blood

neurtoxicty that come from the consumption of the of :

*NADPH , which effects the anabolic process

*NADH , which effects the electron transport chain and phosphorylation process

there are two types of hyperammonemia :

*aquired :certain drugs or certain toxic interfere with urea cyle

*congenital: mutation in the genes that are responsible for the metabolism of urea cycle usually related to x-linked .

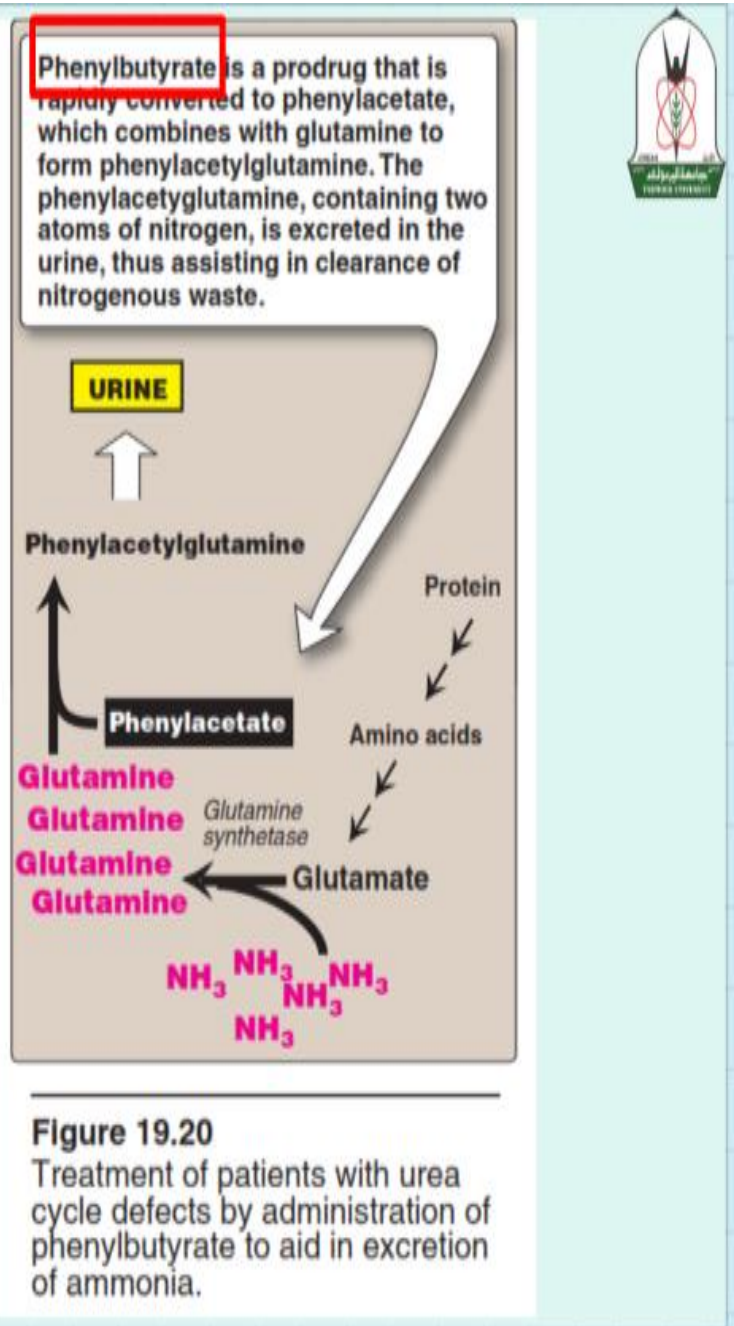


Figure 19.20
Treatment of patients with urea cycle defects by administration of phenylbutyrate to aid in excretion of ammonia.

treatment of patients with hyperammonemia by phenylbutyrate that helping in the consumption of the amonia by the formation of another molecule

if we have high concentration of amonia in the body بدل ما تعطل ال deamination process we will consume the glutamine that will be formed by the toxicity of the amonia

*toxicity of the amonia that come from the conjugation of the glutamate and amonia اللي بتعكس deamination process و بتتحول الى GLUTAMINE(اللي هو المشكلة)

glutamine which is converted into phenylacetylglutamine by conjugation with phenylacetate , which is by the consumption of the drug that known as phenylbutyrate , which is converted by the liver to phenylacetate and then will be conjugated to the glutamine to reduced the toxicity of the amonia.

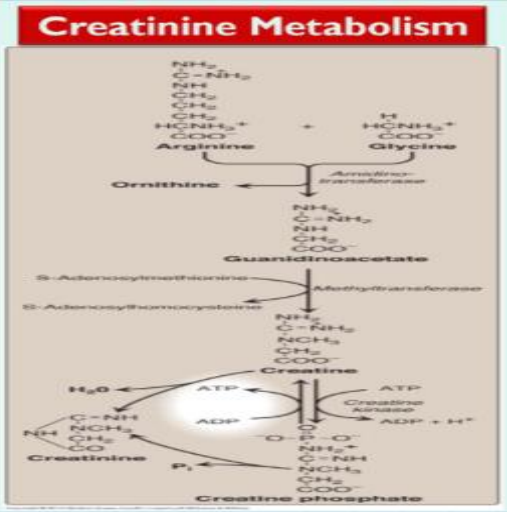
Table 4.2 Causes of an abnormal plasma [urea].

Reduced plasma [urea]	Low protein diet, severe liver disease, water retention
Increased plasma [urea]	
Pre-renal causes	High protein diet, GI haemorrhage ('meal' of blood)
	Any cause of increased protein catabolism (e.g. trauma, surgery, extreme starvation)
	Any cause of impaired renal perfusion (e.g. ECF losses, cardiac failure, hypoproteinaemia)
Renal causes	Any cause (acute or chronic) of a reduced GFR
Post-renal causes	Any cause of obstruction to urine outflow (e.g. benign prostatic hypertrophy, malignant stricture or obstruction, stone)

renal causes is the most important reason for the hyperuremia , that is why the urea is used as parameter in the renal function test

reduced plasma urea is very rare

urea is different from femal to male



creatinine related to creatin that has two form (creatine as free one or creatine phosphate) which is come from conjugation of two precursors (arginine and glycine)

then by will be amidino-transferaseenzyme that will be the formed ornithine and guanidinoacetate that will be converted to creatine by methyltranseferase enzyme (adding methyl group to guanidinoacetate

*the source of the methyl group is the s-adenosylmethionine that will be conerted to s-adenosylhomocysteine

phosphate

parameters that are used in renal function test (creatinine , urea ,Na+,and K+)

the muscles are high energy consumption organ , so the generation of the creatine phosphate molecule by consumption of one ATPmolecule

*العضلات بتفضل تستخدم مركب اخر يحتوي علىphosphateمثلcreatine phosphate بدل ما يضل ATP

لان كمية الطاقة الموجودة بال creatine phosphate أعلى من ATP

ΔG OF creatine phosphate > ΔG OF ATP

the enzyme is responsible of this reaction is CK(creatine-kinase) and there are many types of ck :(MM, MB,BB)
*the most important one is the CK-MB as indicator of myocardial infraction (found in cardiac muscles)

creatinine is indicate there is consumption of the amino acids in the muscles eventully , they will form creatine

creatine and creatine phosphate can be converted to creatinine by :

transfering of inorganic phosphate - dephosphorylation process in order to form the ring structure (creatinine)

dehydration of the creatine

because the sourceof the creatinine in the muscle tissues , there is constant concentration of creatinine in indiviualls , and creatinine is used to check GFR (glumeral filtration rate
)
* degradation of the muscles is very limited , so creatinine concetration is constant .

Table 4.1 Causes of an abnormal plasma [creatinine].

Reduced plasma [creatinine]	
Physiological	Pregnancy
Pathological	Reduced muscle bulk (e.g. starvation wasting diseases, steroid therapy)
Increased plasma [creatinine]	
No pathological significance	High meat intake, strenuous exercise
	Drug effects (e.g. salicylates)
	Analytical interference (e.g. due to cephalosporin antibiotics)
Pathological	Renal causes, i.e. any cause (acute or chronic) of a reduced GFR

reduced plasma (creatinine) could be physilogical (pregnancy) ,the creatinine will be consumed during pregnancy or pathological condition(degradation of muscles due to starvation)

creatinine is different from female to male

(chronic or acute) renal faliure or nephropathy that will affect the GRF and it will associate with increased concentration of creatinine in the blood and reduced it in the renal system