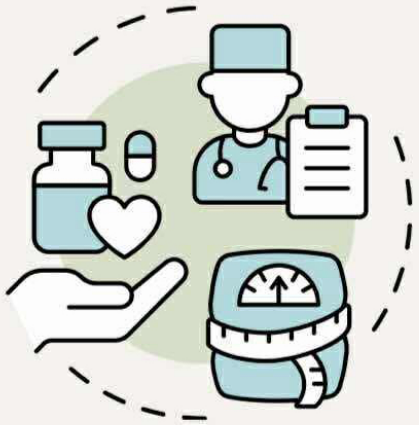
تفريغ كلينكال



المحاضرة: Amino acid metabolism

الصيدلاني/ة: ياسمين خليل

Soul Academy

لجان الدفعات

اللهم اغفر لأيهم وارحمه وعافه وأعف عنه واجمعه

وأهله في الجنة

a.a احماض امينية

building blocks for proteins

Amino acid metabolism and plasma proteins

Amino acids

plasma proteins Hormone
, intracellular proteins, Enzymes
a.a من مصدر غذائي

- Amino acids in blood are used in:
  1. Synthesis of plasma, intracellular and structural proteins

مركبات هي مش بروتينات بس فيها N تبعت a.a

  2. Synthesis of nonprotein nitrogen containing compounds: purines, pyrimidines, porphyrins, creatine, histamine, thyroxine, epinephrine and coenzyme NAD

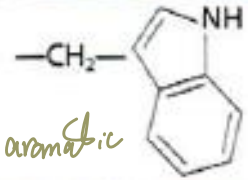
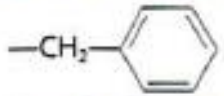
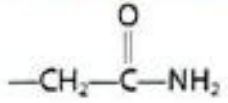
أحد أهم مصادر الطاقة لجسم الإنسان

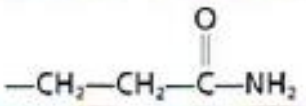
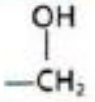
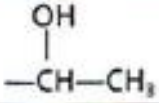
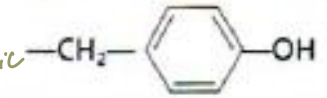
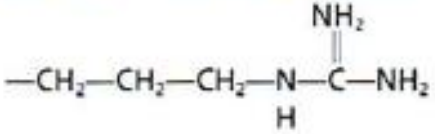
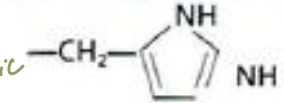
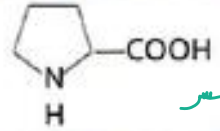
  3. Body energy: 12-20% of energy is due to proteins: by Krebs cycle

عشان نخزن a.a في الجسم بالبول لنحميه N

- The ammonium produced during deamination of amino acids is converted into urea in liver → then goes to urine by kidneys

TABLE 8-1. AMINO ACIDS REQUIRED IN THE SYNTHESIS OF PROTEINS

AMINO ACID	R
Glycine (Gly) non polar	—H The smallest achiral
Alanine (Ala) non polar	—CH_3 The smallest chiral
Valine (Val)* non polar	—CH(CH_3)—CH_3
Leucine (Leu)* non polar	—CH_2—CH(CH_3)—CH_3
Isoleucine (Ile)* non polar	—CH(CH_3)—CH_2—CH_3
Cysteine (Cys)	—CH_2—SH
Methionine (Met)* non polar	—CH_2—CH_2—S—CH_3
Tryptophan (Trp)* non polar	 aromatic
Phenylalanine (Phe)* non polar	 aromatic
Asparagine (Asn) Polar	

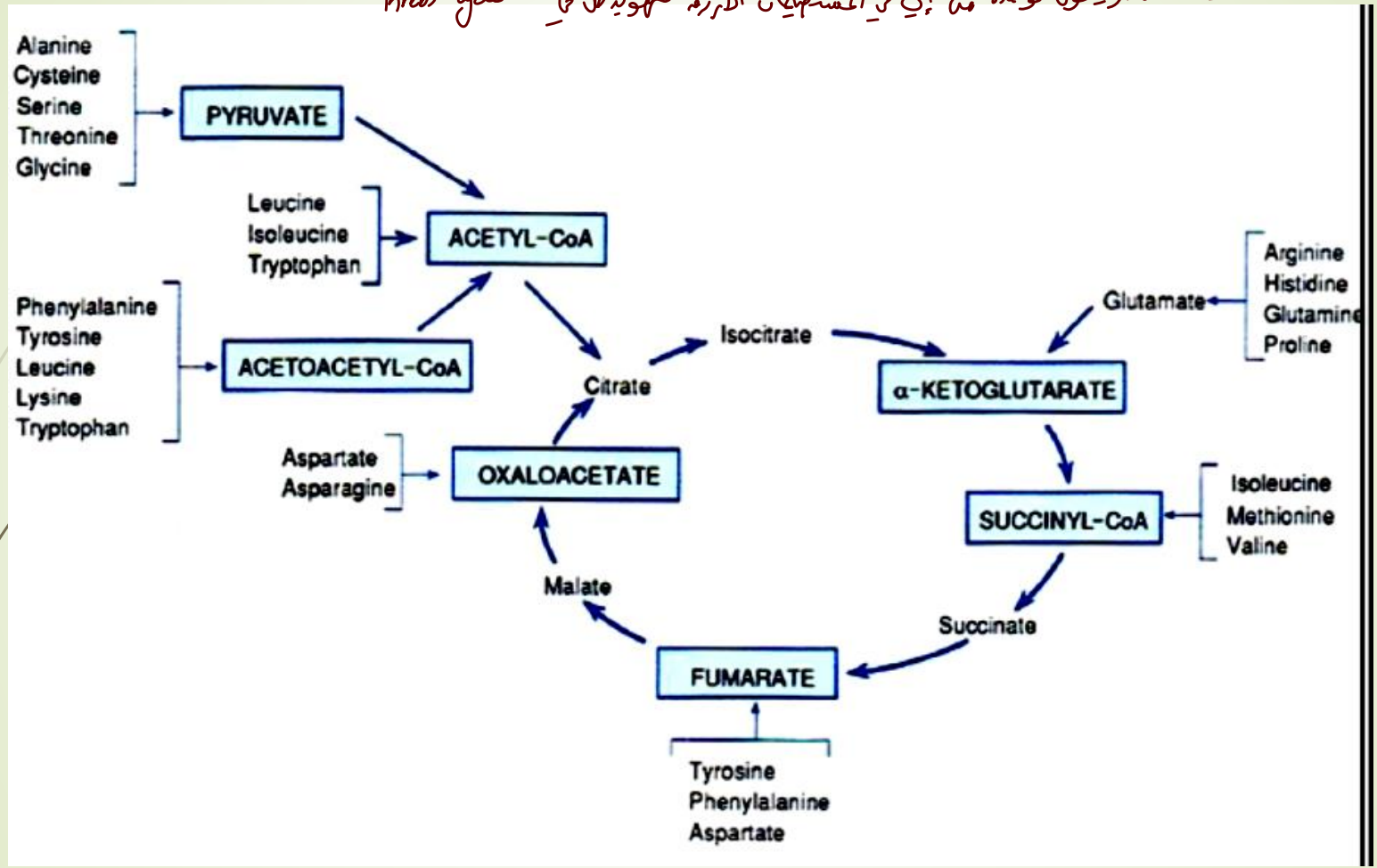
AMINO ACID	R
Glutamine (Gln) Polar	
Serine (Ser) Polar	
Threonine (Thr)* Polar	
Tyrosine (Tyr) Polar aromatic	
Lysine (Lys)* basic	—CH_2—CH_2—CH_2—CH_2—NH_2
Arginine (Arg) basic	
Histidine (His)* basic aromatic	
Aspartate (Asp)	—CH_2—COOH
Glutamate (Glu)	—CH_2—CH_2—COOH
Proline (Pro)† non polar	 الوحيد حلقي يكسر

branched amino acid

Sulfur containing

(—) charge acidic

- أي 9.9 قادر يتحول لوحدة من إلي في المستهلكات الأزرق منهو يدخل في Krebs cycle



الأمراض إلي تصير وسببها a.a

Aminoacidopathies

لحالها يحدث في إنزيم مسؤول عن تحويل a.a = A إلى B و إنزيم يحول B إلى C مثلاً وصار فيه خلل في إنزيم إي

بيشتغل على A حتى يصير B
هون رح يتراكم و يعمل مشاكل.
ف بصير نقص في الجسم من B
وزيادة في A

- Can be in the activity of specific enzyme in the metabolic pathway

يا إنه موجود وكمية طبيعية بس مش شغال، أو موجود بكمية مش كافية
أو غير موجود بالجسم بوصفه لحالة جيني عند الشخص

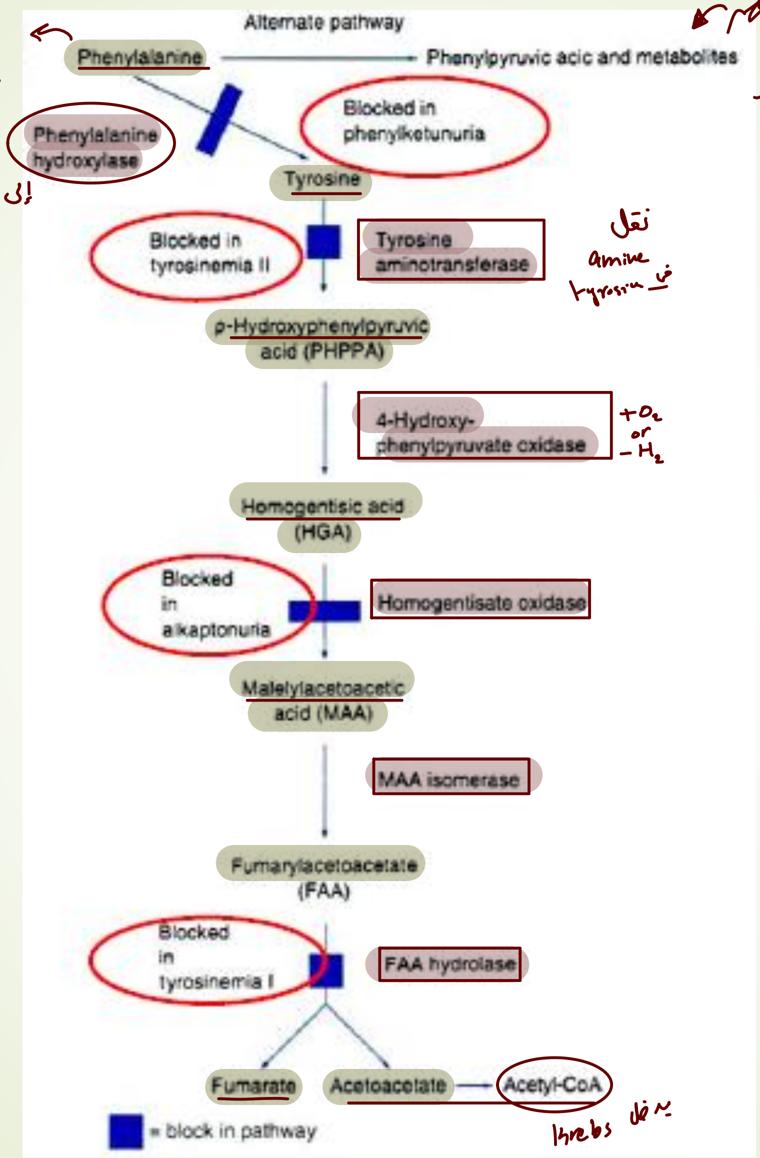
- Membrane transport system for amino acids

ف بيتراكم a.a في مكان وبنقص في مكان آخر

- Diseases to talk about:
  - Phenylketonurea ✓
  - Maple syrup urine disease (MSUD) ✓
  - Homocystinuria ✓
  - Argeninosuccinic aciduria and citrullinemia ✓
  - Cystinurea ✓

essential a.a
من مصدر خارجي ناخذه

هاد الإنزيم يضيف OH إلى phenylal... عشان يصير tyrosine



مهم لفهم التشابتر

نقل amine في tyrosine

$+O_2$ or $-H_2$

يدخل krebs

هاد اللون هو إنزيم

هاد اللون هو مادة ناتجة

يا إخوانه الكبد أي إنه متأثر إذ مرض
رح نحكي عنه هو phenylketonuria
سببه تراكم phenylalanine، طيب ليه تراكم؟
لأنه الإنزيم phenylalanine hydroxylase
مش شغال فـ تراكمت وصار نقص من tyrosine
فـ لو بدي أشرح بحل لهاي المشكلة: أخلي المريض يبعد
عن الأكل ومصادر phenylala ويروح للصيدلية يجيب supple
لـ tyrosine.

فهمتوا ليه المخطط رح يسهل الفهم !.

Phenylketonuria (PKU)

وراثي من الأب والأم (لازم جينين) عشان يكون مصاب أما لو جين ← حامل للمرض

- An autosomal recessive genetic disorder characterized by a deficiency in the hepatic enzyme phenylalanine hydroxylase (PAH)
- The PAH gene is located on chromosome 12

زي ما شفناه فوق

صار على الطفرات مسببة للأمراض بس إلي بنحكي عنه هون هو مسبب للأمراض

- More than **four hundred** disease-causing **mutations** have been found in the PAH gene

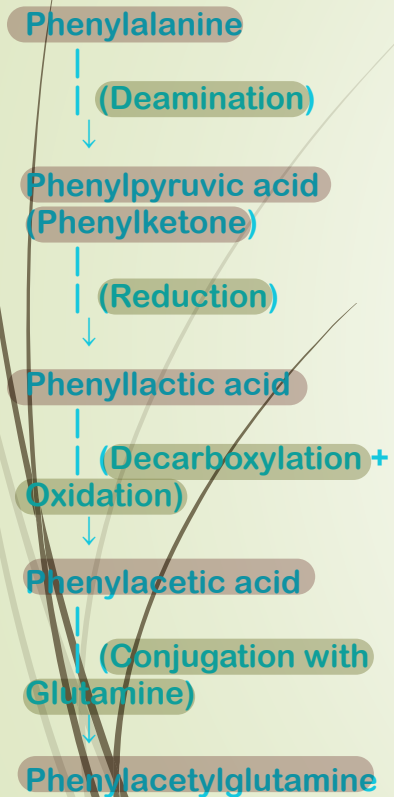
400 احتمال من الطفرات رح تسبب هاد الخلل (حذف، استبدال، إضافة...)

- PAH is necessary to metabolize the amino acid phenylalanine to tyrosine

الحالة في هاد الإنزيم رح تؤدي إلى تراكم phenylalanine إلى أكثر من 1200 µmol/L وبؤدي إلى انتاج مواد سامة ثانية مثل: فحص في السلايد إلي بعد

- When deficient, phenylalanine accumulates to a level > 1200 µmol/L and metabolized by alternative pathways.

Phenylketonuria (PKU)



- The metabolites which are detected in blood and urine include:
- Phenylpyruvic acid (which known as phenylketone): which is the product of deamination of phenylalanine
- phenyllactic acid: which is the reduction product of phenylpyruvic acid
- Phenylacetic acid which is produced by decarboxylation and oxidation of phenylpyruvic acid
- And phenylacetylglutamine: which is the glutamine conjugate of phenylacetic acid
- These metabolites give urine musty odor

normal range: 70 - 200

100 – 600 asymptomatic
600 – 1200 mild
higher than 1200 severe

Phenylketonuria (PKU)

- Variants of the disease result from partial deficiencies of PAH activity and are typically classified as:
  - Mild PKU if phenylalanine levels are between 600 and 1200 µmol/L
  - Non-PKU mild hyperphenylalaninemia which present with phenylalanine levels in the range of 180-600µmol/L and no accompanying accumulation of phenylketones.

- The normal limits for serum phenylalanine levels for full term, normal weight newborns range from 1.2 to 3.4 mg/dL (70-200 µmol/L)

normal

Phenylketonuria (PKU)

- A rarer of the disease occurs when PAH is normal but there is a defect in the biosynthesis of the **cofactor tetrahydrobiopterin (BH4)** by the patient which is necessary for proper activity of the enzyme (for PA, tyrosine and tryptophan hydroxylation)
- It results in hyperphenylalaninemia, that are not responsive to dietary treatment
- Examination of urinary proteins is helpful in diagnosis
- Although cofactor defects are rare, they must be identified so that appropriate treatment can be initiated
- Patients must be given the active cofactor a long with the neurotransmitter precursor L-dopa and 5-OH tryptophan

Phenylketonuria (PKU)

- Left untreated, this condition can cause problems with brain development, leading to progressive mental retardation and seizures
- In infants and children, the deterioration of brain function begins in the second or third week of life
- Brain damage can be avoided if the disease is detected at birth and the infant is maintained on a diet containing very low level of phenylalanine and high levels of tyrosine
- There is no cure. Damage done is irreversible so early detection is crucial

اللهم أعز الإسلام والمسلمين

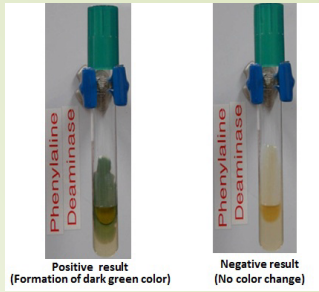
Screening for PKU

- The Guthrie bacterial inhibition assay:
- Spores of the organism Bacillus subtilis are incorporated into an agar plate that contains β2-thienylalanine, a metabolic antagonist to B. subtilis growth.
- A filter paper disk impregnated with blood from the infant is placed on the agar
- If the blood level exceeds the range of 2-4 mg/dL, the phenylalanine counteracts the antagonists and bacterial growth occurs.
- To avoid false-negative results, the infant must be at least 24 hours old to ensure adequate time for enzyme and amino acid levels to develop
- The sample should be taken before administration of antibiotics or transfusion of blood or blood products
- Premature infant can show false positive results due to the immaturity of the liver enzyme systems

Other screening methods

- Microfluorometric assay: The direct measurement of phenylalanine in dried blood filter disks:
  - This method is quantitative, more adaptable to automation, and is not affected by presence of antibiotics.
- The procedure is based on the fluorescence of complex formed of phenylalanine-ninhydrin-copper in the presence of dipeptide (i.e. L- leucyl-L-alanine).
- The test requires pretreatment of the filter paper specimen with trichloacetic acid (TCA)
- The extract is then reacted with microtiter with a mixture of ninhydrin, succinate, and leucylalanine in the presence of copper tartarate.
- The fluorescence of the complex is measured using excitation/ emission wavelengths of 360 nm and 530 nm, respectively
- For quantitative methods, HPLC or tandem mass spectrometry (MS/MS) are used

Other screening methods



- Urine testing for phenylpyruvate can be used for diagnosis in questionable cases and for monitoring of dietary therapy
- The test which may be performed by tube or reagent strip test involves the reaction of ferric chloride with phenypyruvic acid in urine to produce a green color
- Prenatal diagnosis and detection of carrier status in families with PKU is now available using DNA analysis
- Analysis using cloned human PAH cDNA, has revealed the presence or numerous restriction fragment length polymorphism in the PAH gene