33

carbohydratesisomersketone starchlipidproteinamine

Biochemistry

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

Done By

Abdallah Kharabsheh

Contributed in the Scientific Correction

Ahmad Izzidin 😊

Contributed in the Grammatical Correction

Doctor

Diala Abu Hassan

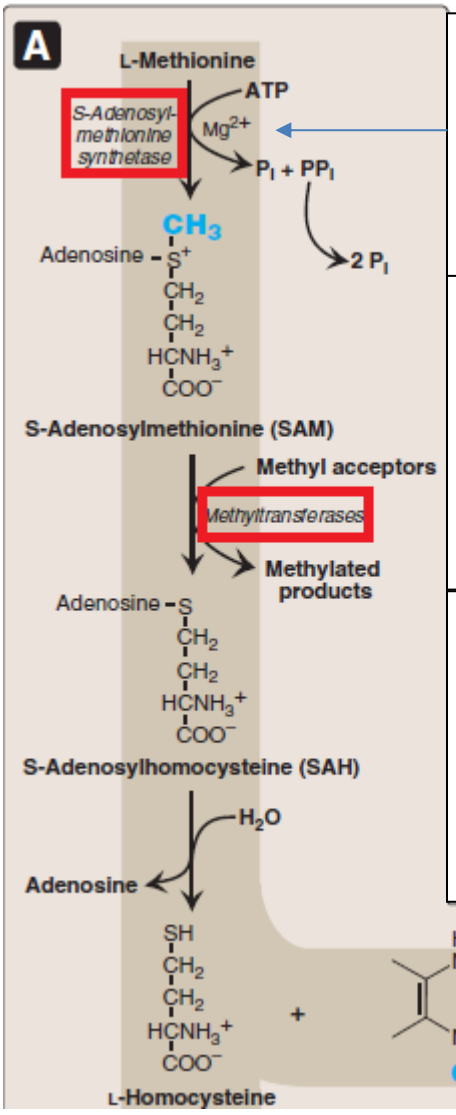
Methionine Metabolism

Methionine is an important amino acid because:

i) it's the first amino acid to be added during protein synthesis (translation process).
ii) During Methionine metabolism, the Methyl donor S-Adenosylmethionine (SAM) is produced, and it is important for many methylation reactions.
iii) Methionine is an essential amino acid used to produce the non-essential amino acid Cysteine.

Synthesis of SAM:

- Synthesis of SAM (a high-energy compound that has no phosphate) requires ATP.
- When Adenosine is added to Methionine, Methionine's Methyl group gets activated. And now it's ready to get transferred to an acceptor molecule, such as norepinephrine in the synthesis of epinephrine.
- Methyl group is transferred to O, N, or C atoms.
- Methyl transfer is irreversible because of free energy loss.
- When SAM loses its methyl group, S-Adenosylhomocysteine (SAH) is formed.



Notice that, the source of Adenosine in SAM is an ATP molecule.

Adenosine is considered a nucleoside; A nucleotide without the phosphate groups.

Adenosine is added on the sulfur atom of methionine; hence its name SAM.

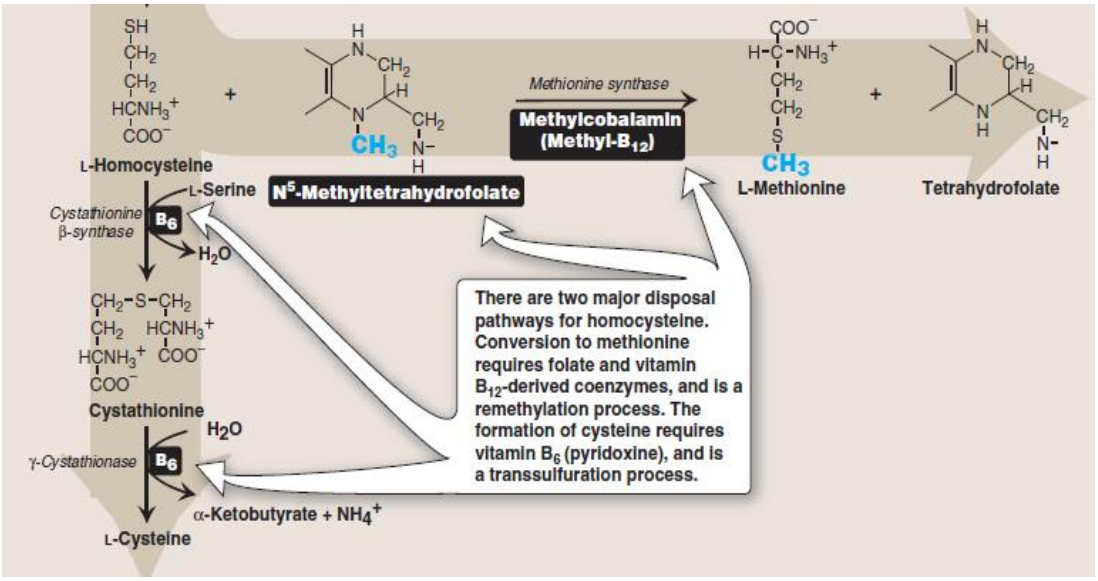
- SAH can be hydrolyzed to homocysteine and adenosine.

Homocysteine fates:

A) Re-methylation if Met is deficient to reproduce Met.
B) Transulfuration pathway if Met is available, to convert Homocysteine to Cys.

Homocysteine is a considered branching point; it can either proceed to the production of Cysteine, or to the reproduction of Methionine depending on the availability of enzymes and cofactors (Methionine production requires Vitamin B12 and n5-methyltetrahydrofolate (methyl donor) as cofactors, while Cysteine production requires Vitamin B6 as a cofactor).

Study this picture thoroughly



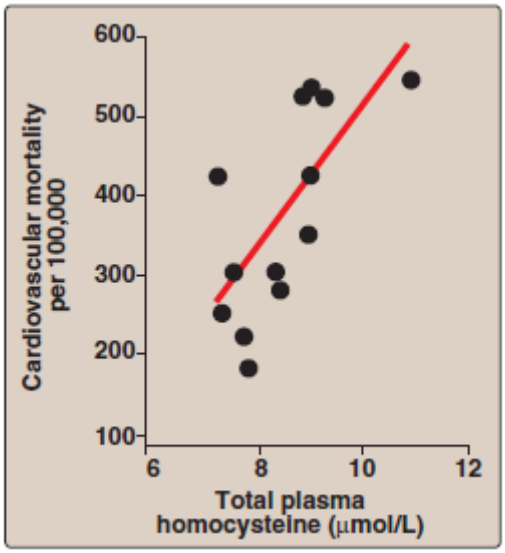
Notice the branching point for the synthesis of Methionine and Cysteine.

- The resulting α-ketobutyrate undergoes oxidative decarboxylation to form propionyl CoA that is then converted to succinyl CoA.

Clinical hint:

Homocysteine and vascular disease

High homocysteine level promotes oxidative damage, inflammation, endothelial dysfunction and increases risk for occlusive vascular disease.
Homocysteine levels are inversely related to levels of folate, B12, and B6.
Elevated homocysteine or decreased folic acid levels during pregnancy increases the incidence of neural tube defects (improper closure, as in spina bifida) in the fetus.



- Vitamin B12 is a cofactor needed for the production of Methionine from Homocysteine.
- Vitamin B12 deficiency leads to:
    1. decrease this reaction's rate, so Methionine levels will be decreased, and Homocysteine will start to accumulate.
    2. Body will try to compensate by the increased production of cysteine, but eventually, Homocysteine will accumulate.
- There is a statistical correlation between the increased blood levels of Homocysteine and many other diseases (eye, GI, and more specifically Cardiovascular diseases).
- It is not for sure that homocysteine level is actually a risk factor for these diseases, it is just a statistical hypothesis.
- Vitamin B12 should be given as a supplement for Vitamin B12 deficient people, to improve the rate of the reaction (Methionine production from Homocysteine).

- N5-methyltetrahydrofolate is another cofactor for the previous reaction.
- N5-methyltetrahydrofolate is the active form of folic acid (Vitamin B9) [source is green leafy vegetables].
- Folic acid deficiency is less common than Vitamin B12 deficiency in our region, because of the folic acid fortified flour and wheat products.
- Folic acid increases fertility for women.
- when a woman is planning to get pregnant, she should take folic acid supplementation for 3 months before pregnancy and for 3-6 months while pregnant, to prevent developmental deformities especially of the Nervous system and spinal cord (spina bifida).

Amino acids that form acetyl CoA or acetoacetyl CoA:

Phenylaniline and Tyrosine produce acetoacetate during their catabolism.
Leucine: is exclusively ketogenic (acetoacetate and acetyl CoA).
Isoleucine: is both ketogenic and glucogenic (acetyl CoA, acetoacetyl CoA and succinyl CoA).
Lysine: is exclusively ketogenic (acetyl CoA and acetoacetyl CoA).
Tryptophan: is both glucogenic and ketogenic (acetyl CoA and acetoacetyl CoA).

Note: A glucogenic amino acid is an amino acid that can be converted into glucose through gluconeogenesis. While a ketogenic amino acid is an amino acid that can be degraded directly into acetyl-CoA, which is the precursor of ketone bodies.

Leu and Lys ➔ exclusively ketogenic

Aromatic (Phe, Tyr and Trp) and Ile ➔ ketogenic and glucogenic (have other products as well)

Role of Folic acid in amino acid metabolism

Folic acid and SAM: molecules that can carry one-carbon unit. So, the difference between reactants and products is one carbon ***(e.g. glycine + Methyltetrahydrofolate ➔ serine + tetrahydrofolate)***

- Tetrahydrofolic acid (THF) is the active form of folic acid (doesn't participate in the reaction, it's rather ready to carry one carbon unit).
  - ***We depend on SAM when we need the extra carbon in the form of methyl group (CH3).***
  - ***In other reactions, we may use tetrahydrofolate.***
- THF is produced from folate by dihydrofolate reductase in a two-step reaction requiring two NADPH.
- The carbon unit carried by THF is bound to nitrogen N_5 or N_{10}, or to both N_5 and N_{10}.
- One-carbon compounds bound to THF can be recognized and manipulated by biosynthetic enzymes.

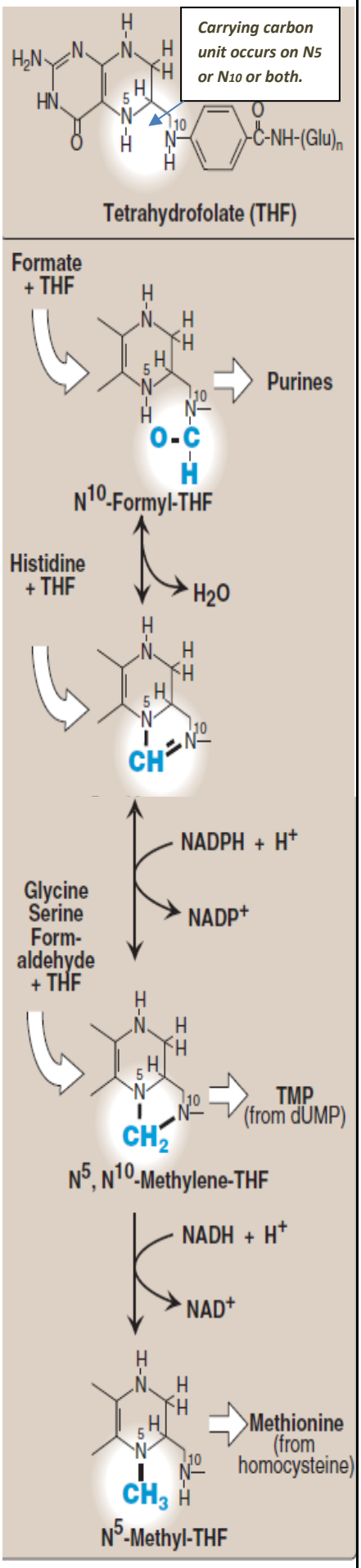
  A) If carbon is connected to N_{10} (in the form of formyl), it will be called N_{10}-Formyl-THF and it's important in the synthetic process of purines nucleotides -Adenine or Guanine-.

  B) By dehydration of N_{10}-Formyl-THF, carbon is connected to N_5 and N_{10} -*single bond, double bond respectively*- and the molecule is called N_5,N_{10}-methenyl-THF.

  C) A reduction reaction by NADPH dependent reductase, converting Methenyl into Methylene. (N_5, N_{10}-Methylene-THF is important in the synthesis of thymine pyrimidine).

  D) Another reductase introduces a hydrogen atom breaking the double bond to form N_5-methyl-THF which is used in many reactions including the reproduction of methionine.

- Folate deficiency presents as a megaloblastic anemia due to decreased availability of the purines and of the TMP needed for DNA synthesis.



- Jordanians, Caucasian, Circassians, Chechens and many other regions have high levels of Methylene-THF Reductase (MTHFR) -which catalyzes the production of N^5-Methyl-THF-. Deficiency of this enzyme due to a mutation is considered a polymorphism because it is prevalent in more than 1% of the population.
- Some studies showed a relation between MTHFR mutations and cancer.
- many reactions which contain THF as a carbon unit carrier are reactions of nucleotides synthesis, so a mutated enzyme will lead to stop synthesis of nucleotides, and cell division -which depends on nucleotides to build DNA and replication - will stop as a result.
- that's why there is a statistical relationship between MTHFR mutations and some types of cancer.
- the most common cancer patients like breast or lung cancer show higher levels of MTHFR mutations than normal people.
- also, it is not approved to be a risk factor for cancer, it is just a statistical correlation.
- giving folic acid as supplementation to MTHFR deficient people may increase the problem, because it will accumulate, so the solution is by giving methyl-THF supplementation.

Biosynthesis of Nonessential Amino Acids

You will notice that the Biosynthesis of Nonessential Amino Acids pathways are repeated, because the degradation of one amino acid is a biosynthetic pathway of another amino acid.

Essential AAs: Phe, Val, Thr, Trp, Met, Leu, Ile, Lys & His
Nonessential AAs (starts with A, C, G): Ala, Arg, Asp, Asn, Cys, Glu, Gln, Gly, ***Pro, Ser & Tyr (exception)***

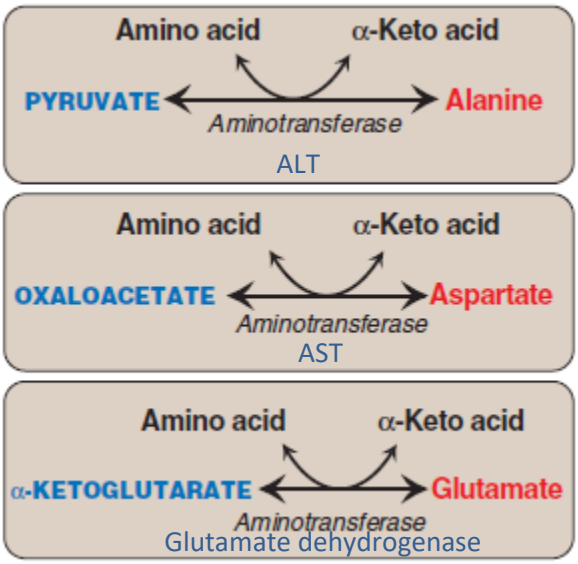
Nonessential amino acids are synthesized from:

I) Metabolic intermediates.
II) From essential amino acids (Ex: Tyr and Cys are synthesized from Phe and Met, respectively).

synthetic reactions for the nonessential amino acids: -

A) Synthesis from α-ketoacids through transamination.

Ala, Asp, and Glu are synthesized by transfer of an amino group to the α-ketoacids; pyruvate, oxaloacetate, and α-ketoglutarate, respectively. Glu can also be synthesized by the reversal of oxidative deamination, catalyzed by glutamate dehydrogenase.

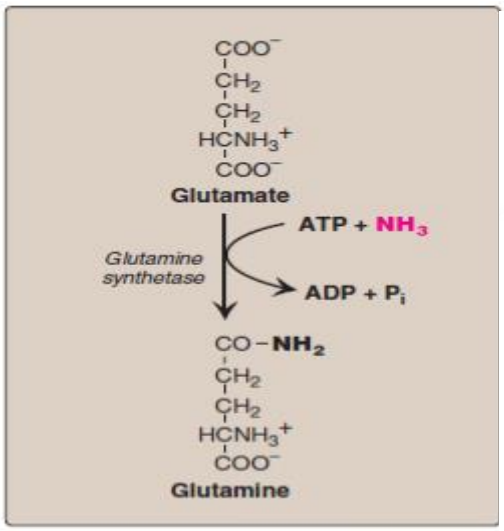


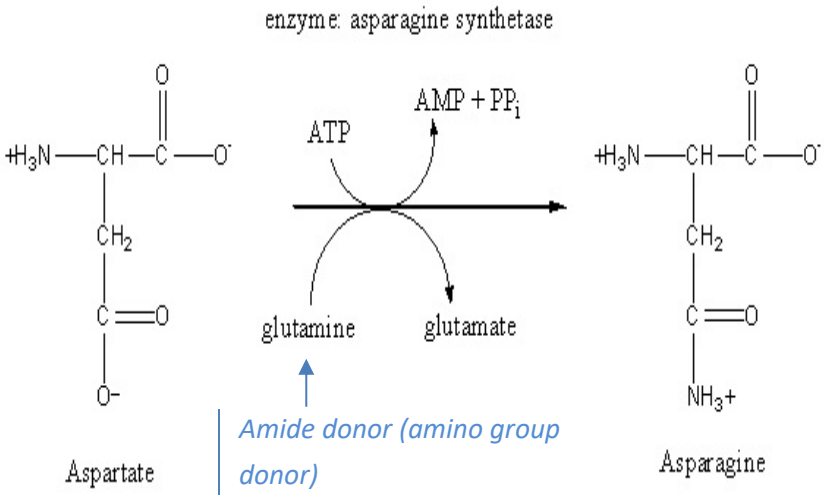
B) Synthesis by amidation

- ***Amino acids that end with the suffix "ine" like glutamine or asparagine contain an extra amino group.***
- ***Amino acids that end with the suffix "ate" like aspartate or glutamate contain an extra carboxylic group.***
- ***Amino group + carboxylic group ➔ amide linkage.***

I) Glutamine (Gln) is formed from glutamate (Glu) by glutamine synthetase.

II) Asparagine (Asn) is formed from Aspartate (Asp) by asparagine synthetase, using glutamine as the amino group donor (by deamination of glutamine).





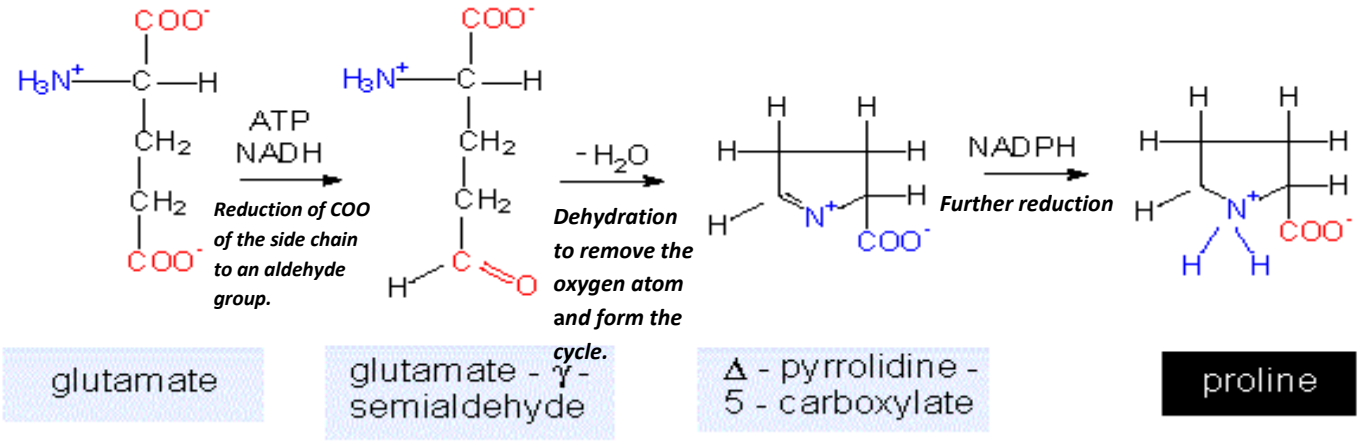
- Why is glutamine used as the amino group donor?

Because, all amino acids are converted to glutamine (for NH_3 transport purposes) in all tissue -except for the muscles that have alanine cycle-, that's why we have high concentrations of Gln used in the productive pathway of asparagine in cases of ammonia deprivation

C)Proline

> ***Remember, proline is metabolized into glutamate and then α-ketoglutarate.***
> ***Proline is also synthesized from glutamate but, synthesis and metabolism of proline are not the exact reverse reaction.***

- Glutamate is converted to proline by cyclization and reduction reactions.

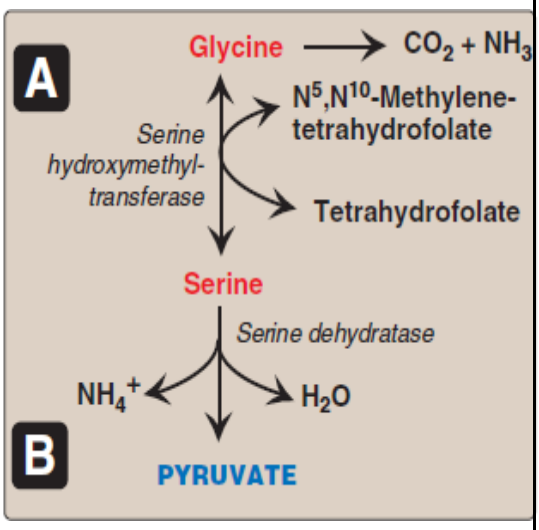


D) Serine, glycine, and cysteine

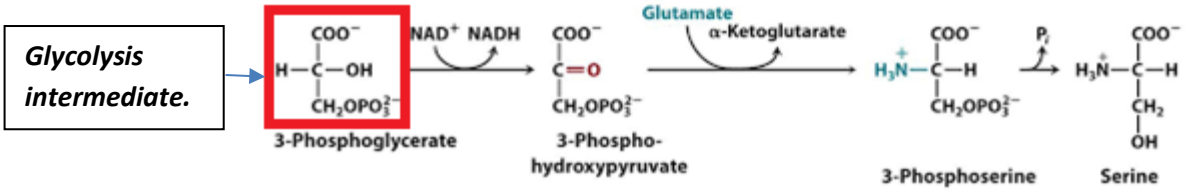
- Ser can be formed from:

A) glycine hydroxymethylation through transfer of a hydroxymethyl group by serine hydroxymethyl transferase.

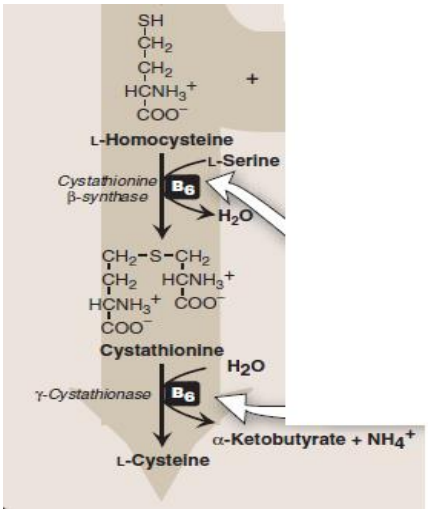
-N_5,N_{10}-methylene-THF is the one carbon donor.



B) Ser arises from 3-phosphoglycerate that is oxidized to 3-phosphopyruvate, and then transaminated to 3-phosphoserine. Serine is formed by hydrolysis of the phosphate ester.



- Gly is synthesized from:
  A) serine by removal of a hydroxymethyl group. ***-THF is the one carbon acceptor.***
  B) also, by serine hydroxymethyl transferase.



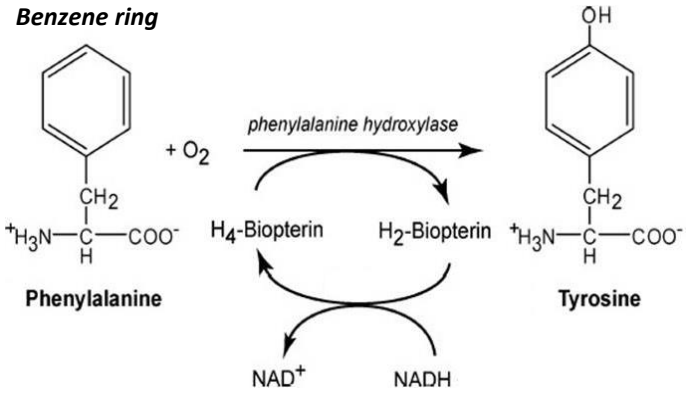
- Cys is synthesized by two consecutive reactions in which homocysteine combines with serine, forming a large complex cystathionine by the action of *cystathionine β-synthase* that is hydrolyzed by the action of *γ-cystathionase* to α-ketobutyrate and Cys.

Homocysteine is derived from Met.
Because Met is an essential amino acid. the Met dietary intake is adequate.

E) Tyrosine

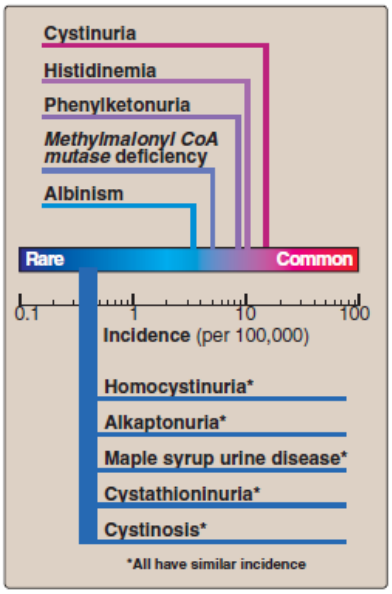
Made from a very similar structure AA (Phe).

Benzene ring ***Phenyl group***



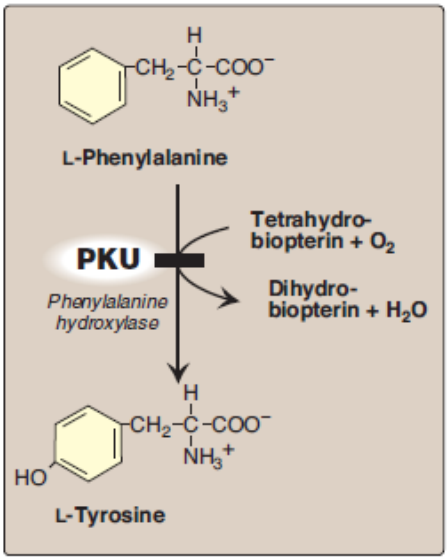
- Tyr (non-essential AA) is formed from Phe (essential AA) by phenylalanine hydroxylase.
- The reaction requires molecular oxygen and the coenzyme tetrahydrobiopterin (BH4) which will be converted to the oxidized form (BH2) and recycled by reduction reaction (oxidation of NADH)
- BH4 can be synthesized from GTP
- One atom of molecular oxygen becomes the hydroxyl group of Tyr, and the other atom is reduced to water.
- BH4 is oxidized to dihydrobiopterin (BH2).
- BH4 is regenerated from BH2 by NADH-requiring dihydro pteridine reductase.

Metabolic defects in amino acid metabolism



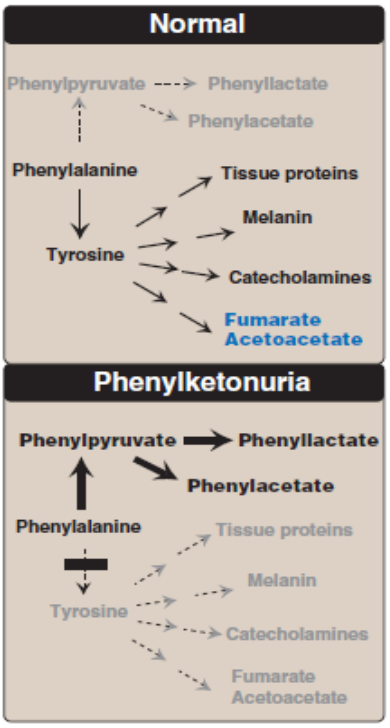
The inherited defects of AA metabolism if stayed untreated results in mental retardation or other developmental abnormalities because of the harmful accumulation of metabolites.

Metabolic disorders: Phenylketonuria (PKU)



- The most common inborn error of amino acid metabolism (prevalence 1:15,000).
- Due to phenylalanine hydroxylase deficiency.
- Biochemical changes: accumulation of phenylalanine (and a deficiency of tyrosine).
- Tyr cannot be synthesized from Phe and becomes an essential amino acid.
- Caused by any of 100 or more different mutations in the gene that codes for phenylalanine hydroxylase (PAH).

Characteristics of classic PKU:



1) Elevated phenylalanine in tissues, plasma, and urine.
2) The characteristic musty "mousey" urine odor due to phenyllactate, phenylacetate, and phenylpyruvate produced from elevated Phe.
3) CNS symptoms due to phenyllactate, phenylacetate, and phenylpyruvate crossing the Blood Brain Barrier: Mental retardation (IQ < 50) due to accumulation in the neurons and destroying them, failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow.
4) Hypopigmentation: fair hair, light skin color, and blue eyes because the hydroxylation of Tyr by tyrosinase (the first step in melanin formation) is competitively inhibited by the high levels of Phe.

- Tyrosine becomes an essential amino acid, so they have to get it in adequate quantities from diet or they will have deficiencies in the products of tyrosine (e.g. melanin pigment, epinephrine, dopamine, etc.)

- During the pregnancy, the fetus remains normal because the mother's enzymes compensate his deficiency.

- The problem starts to appear after the baby is born and starts consuming milk which contains proteins, and due to digestion of those enzymes Phe starts to accumulate.

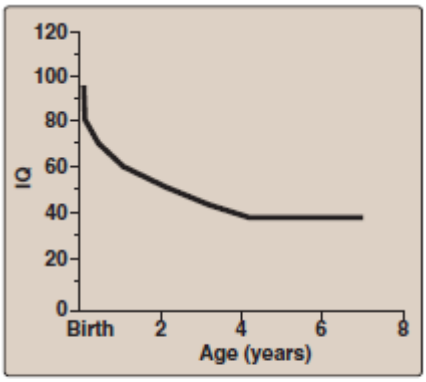


Figure 20.18
Typical intellectual ability in untreated PKU patients of different ages.

Neonatal screening and diagnosis of PKU:

- PKU is treatable by dietary restriction.
- Lack of neonatal symptoms.
- At birth, infants with PKU have normal blood levels of Phe because the mother clears the extra Phe through placenta.
- Exposure protein feeding for 24–48 hours elevates Phe, thus, screening should be done after this to avoid false negatives.

Treatment:

- Dietary restriction: synthetic amino acid preparations low in Phe, supplemented with natural foods low in Phe content (fruits, vegetables, and certain cereals).
- Breast feeding must be converted to a special formula that doesn't contain Phe.
- Earlier treatment (prevents neurologic damage days of life) prevents neurologic complications (mental retardation).
- Aspartame should be avoided since it contains Phe.
- They have to keep this dietary restriction for life, because if they discontinue restricted diet, their IQ will fall.

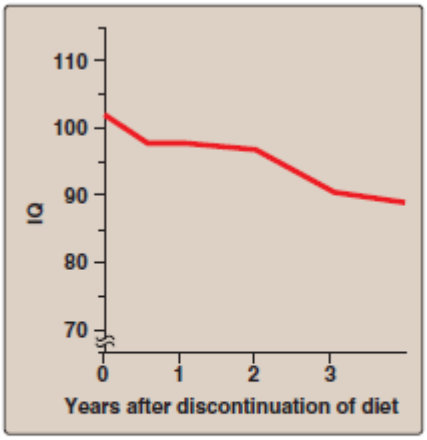


Figure 20.19
Changes in IQ scores after discontinuation of low-phenylalanine diet in patients with phenylketonuria.

Maternal PKU:

- High blood Phe levels in the mother cause microcephaly, mental retardation and heart congenital abnormalities.
- Phenylalanine is a teratogen (***google:*** an agent or factor that causes malformation of an embryo.)
- Dietary control of blood phenylalanine must begin prior to conception and must be maintained throughout the pregnancy.

The next slide was not discussed in the lecture:

Amino acid metabolism and single amino acid groups

Some synthetic pathways require the addition of single carbon groups

Single carbon groups exist in a variety of oxidation states, including formyl, methenyl, methylene, and methyl.

Single carbon groups can be transferred from carrier compounds such as THF and SAM to molecules that are being synthesized

Good luck