GLUCOGENIC & KETOGENIC AMINO ACIDS

BIOCHEMISTRY

All tissues have some capability for synthesis of:

- The non-essential amino acids,
- Amino acid remodeling,
- and Conversion of non-amino acid carbon skeletons into amino acids and other derivatives that contain nitrogen.
- Liver is the major site of nitrogen metabolism in the body.

In times of dietary surplus, the potentially toxic nitrogen of amino acids is eliminated via:

- Transaminations,
- Deamination,
- and Urea formation;

The carbon skeletons are generally conserved as:

- Carbohydrate, via gluconeogenesis,
- or as Fatty acid via fatty acid synthesis pathways.

- These pathways converge to form seven intermediate products:

- **oxaloacetate, α-ketoglutarate, pyruvate, fumarate, succinyl coenzyme A (CoA) , acetyl CoA, and acetoacetate**

- These products directly enter the pathways of intermediary metabolism, resulting either in the synthesis of **glucose or lipid** or in the production of energy through their oxidation to CO_2 and water by the citric acid cycle

Amino acids fall into three categories:

- **GLUCOGENIC**,
- **KETOGENIC**, OR
- **GLUCOGENIC AND KETOGENIC**

GLUCOGENIC

- Glucogenic amino acids are those that give rise to a net production of **pyruvate** or TCA cycle intermediates, such as **α-ketoglutarate , succinyl CoA, Fumarate and oxaloacetate**, all of which are precursors to glucose via gluconeogenesis.

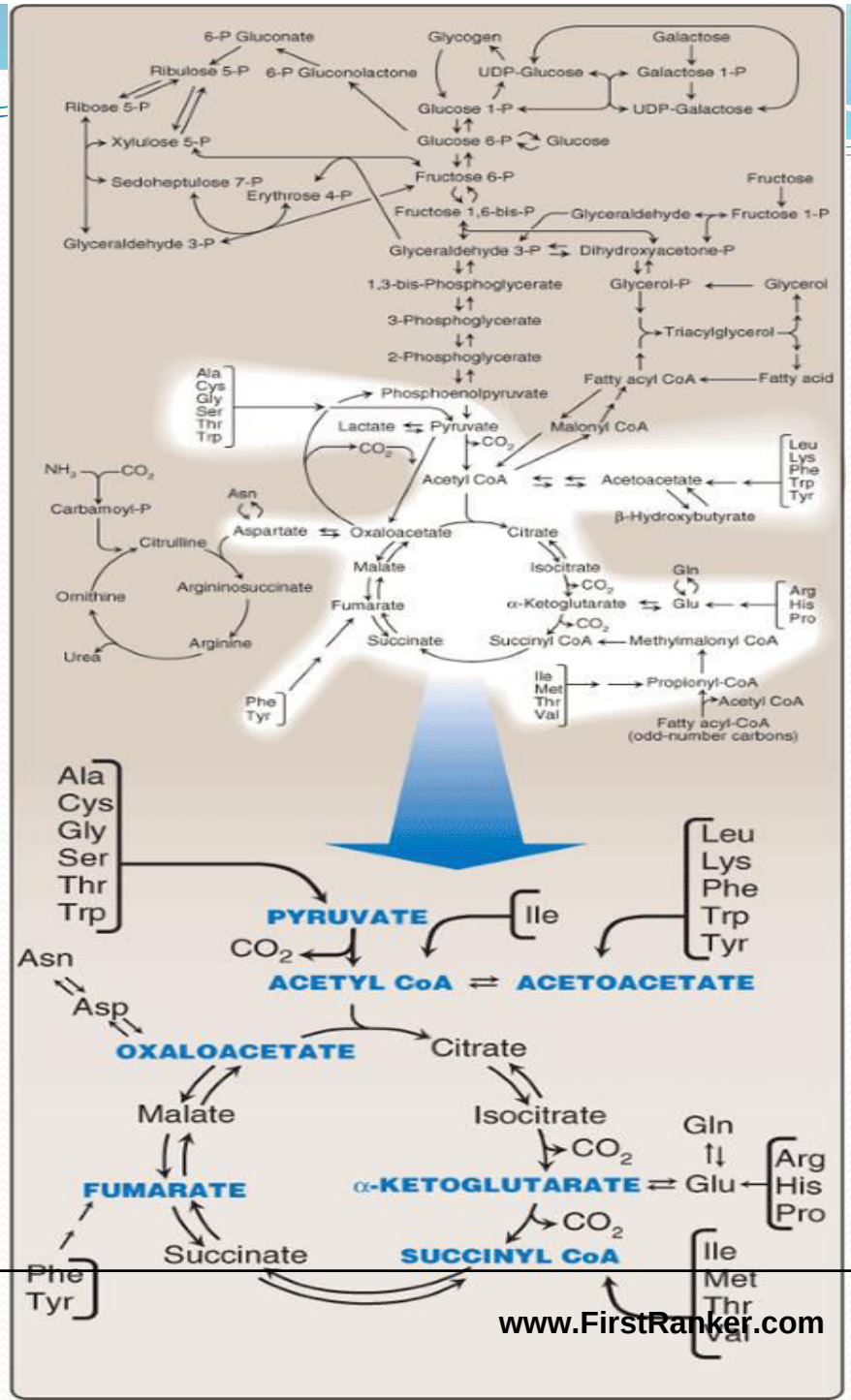
- All amino acids except lysine and leucine are at least partly glucogenic.

KETOGENIC,

- Lysine and leucine are the only amino acids that are solely ketogenic, giving rise only to **acetylCoA or acetoacetylCoA,** neither of which can bring about net glucose production.

GLUCOGENIC AND KETOGENIC

- A small group of amino acids comprised of **isoleucine, phenylalanine, threonine, tryptophan, and tyrosine** give rise to both glucose and fatty acid precursors and are thus characterized as being glucogenic and ketogenic.



	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Essential	Histidine Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Essential vs. Nonessential Amino Acids

Nonessential Essential:

- Alanine
- Asparagine
- Aspartate
- Cysteine
- Glutamate

- Glutamine
- Glycine
- Proline
- Serine
- Tyrosine

Essential:

- Histidine
- Isoleucine
- Leucine
- Lysine

- Methionine
- Phenylalanine
- Threonine
- Tyrptophan
- Valine

amino acid	made from	degraded to	glyco / keto	comments
alanine	pyruvate	pyruvate	glycogenic	large amount in cells
arginine	glutamate	glutamate	glycogenic	strongly basic, urea cycle
asparagine	aspartate	aspartate	glycogenic	glycoproteins
aspartate	oxaloacetate	oxaloacetate	glycogenic	acidic, large amount in cells
cysteine	(methionine) *	pyruvate	glycogenic	-SH group
glutamate	oxoglutarate	oxoglutarate	glycogenic	acidic, very large amount in cells

glycine	serine	one-carbon pool***	glycogenic	no side chain, collagen
histidine	essential	glutamate	glycogenic	weak base
isoleucine	essential	acetyl-CoA + propionyl-CoA	mixed	branched side-chain
leucine	essential	acetyl-CoA	ketogenic	branched side-chain
lysine	essential	not known	ketogenic	long side chain, basic
methionine	essential	propionyl-CoA	glycogenic	contains sulphur, methyl donor
phenylalanine	essential	tyrosine	mixed	aromatic, phenylketonuria

proline	glutamate	glutamate	glycogenic	imino acid
serine	phosphoglycerate	pyruvate	glycogenic	-OH group
threonine	essential	disputed****	glycogenic	-OH group
tryptophan	essential	not known	mixed	aromatic
tyrosine	(phenylalanine)**	fumarate + acetoacetate	mixed	aromatic, phenolic
valine	essential	propionyl-CoA	glycogenic	branched side-chain

- The amino acids **arginine**, **methionine** and **phenylalanine** are considered essential for reasons not directly related to lack of synthesis.

- Arginine is synthesized by mammalian cells but at a rate that is insufficient to meet the growth needs of the body and the majority that is synthesized is cleaved to form urea.

- Methionine is required in large amounts to produce cysteine if the latter amino acid is not adequately supplied in the diet.

- Similarly, phenylalanine is needed in large amounts to form tyrosine if the latter is not adequately supplied in the diet.

AA that form Oxaloacetate

- **Asparagine**(asparagine is hydrolysed by asparaginase liberating ammonia and aspartate- Asparagine necessary for leukemic cells. Asparagine can be given systemically which lowers the levels of asparagine)

- Aspartate (Transamination)

AA that form α-ketogluatrate

- Glutamine(glutamate)
- Proline(glutamate---KG)
- Arginine(by arginase to ornithine---KG)
- Histidine(FIGlu- deficiency of folic acid)

Histidine--------urocanic acid----FIGlu-----glutamate

(TH_4----N-formiminoglutamate)

HISTIDINE:

- Histamine

- Histidase - urocanic acid – N-formimino glutamic acid – glutamate/TH4

- N-formimino glutamate (**FIGlu** – increase in urine in folic acid deficiency)

AA that form Pyruvate

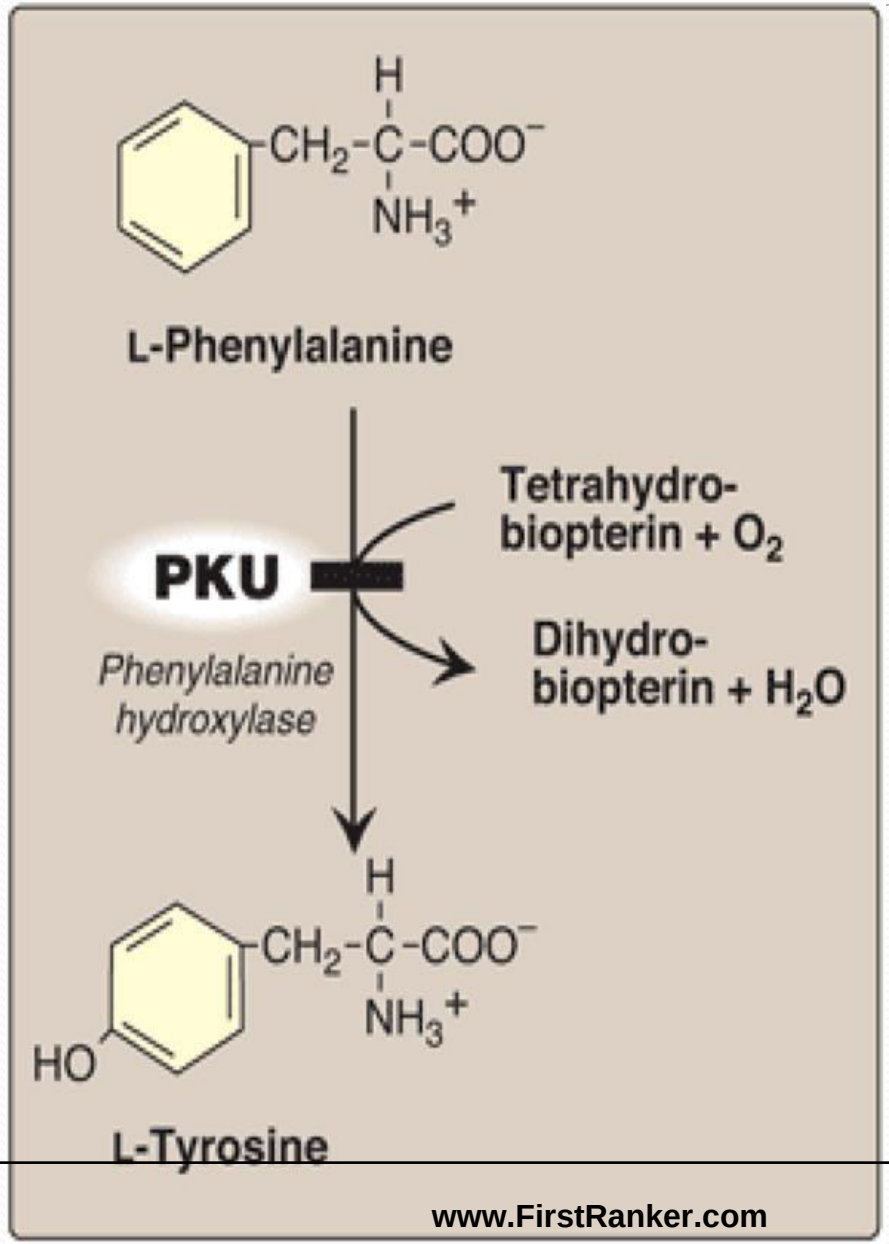
- **Alanine**
- **Serine (glycine +methylenetetrahydrofolate)**
- **Glycine (addition of methyl group forms serine)**
- **Cystine (by desulfuration forms pyruvate)**
- **Threonine**

AA that form Fumarate

- **Phenylalanine**
- **Tyrosine**

- **Ultimately lead to the formation of fumarate and acetoacetate**

- **They are glucogenic and ketogenic**



AA that form Succinyl CoA

- **Methionine**
- **Valine**
- **Isoleucine**
- **threonine**

- **METHIONINE:**
- S- adenosylmethionine – major methyl group donor in one carbon metabolism
- Converted to homocysteine- atherosclerosis.

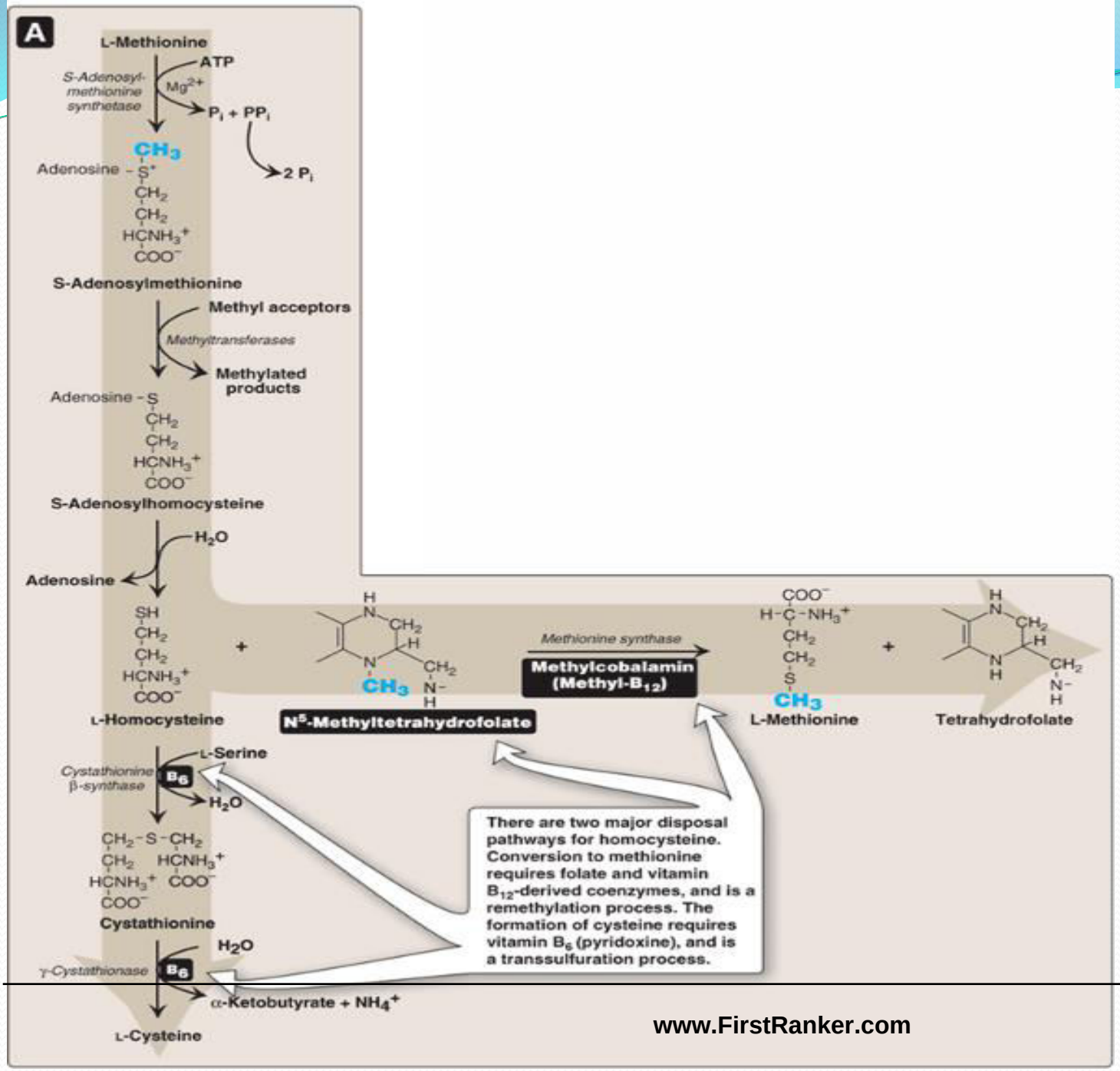
- Methionine condenses with adenosine triphosphate (ATP), forming **SAM**—a high-energy compound that is unusual in that it contains no phosphate.

- The **methyl group** attached to the tertiary sulfur in SAM is "**activated**," and can be transferred to a variety of acceptor molecules, such as norepinephrine in the synthesis of epinephrine

- After donation of the methyl group, S-adenosylhomocysteine is hydrolyzed to homocysteine and adenosine.

- Homocysteine has two fates. If there is a deficiency of methionine, **homocysteine may be remethylated to methionine .**

- If methionine stores are adequate, homocysteine may enter the transsulfuration pathway, where it is **converted to cysteine**.



- Homocysteine accepts a methyl group from N^5-methyltetrahydrofolate (N^5-methyl-THF) in a reaction requiring methylcobalamin, a coenzyme derived from vitamin B_{l2}

- **The methyl group is transferred from the B_{12} derivative to homocysteine, and cobalamin is recharged from N^5-methyl-THF.**

- **Homocysteine condenses with serine, forming cystathionine, which is hydrolyzed to α-ketobutyrate and cysteine**

- This vitamin B_6–requiring sequence has the net effect of converting serine to cysteine, and homocysteine to α-ketobutyrate, which is oxidatively decarboxylated to form propionyl CoA.

- Propionyl CoA is converted to succinyl CoA

Relationship of homocysteine to vascular disease:

- Elevations in plasma homocysteine levels promote **oxidative damage, inflammation, and endothelial dysfunction**, and are an independent risk factor for occlusive vascular disease

- Mild elevations are seen in about 7% of the population.

- Epidemiologic studies have shown that plasma homocysteine levels are inversely related to plasma levels of folate, B_{12}, and B_6

- Large elevations in plasma homocysteine as a result of rare deficiencies in cystathionine β-synthase are seen in patients with **classic homocystinuria**.

- These individuals experience premature vascular disease, with about 25% dying from thrombotic complications before 30 years of age

- Elevated homocysteine levels in pregnant women are associated with increased incidence of **neural tube defects** (improper closure, as in spina bifida) in the fetus.

- Periconceptual supplementation with folate reduces the risk of such defects.

AA that form Acetyl CoA

- Lecine
- Isoleucine
- Lysine
- Tryptophan
- Phenylalanine
- Tyrosine

- **Leucine**: This amino acid is exclusively ketogenic in its catabolism, forming acetyl CoA and acetoacetate
- **Lysine**: An exclusively ketogenic amino acid

- **Isoleucine**: This amino acid is both ketogenic and glucogenic, because its metabolism yields acetyl CoA and propionyl CoA
- **Tryptophan**: This amino acid is both glucogenic and ketogenic because its metabolism yields alanine and acetoacetyl CoA

Catabolism of the branched-chain amino acids

- The branched-chain amino acids, **isoleucine, leucine, and valine**, are essential amino acids. In contrast to other amino acids

- they are metabolized primarily by the peripheral tissues (particularly muscle), rather than by the liver

- **Transamination**
- **Oxidative decarboxylation (branched chain α keto acid dehydrogenase – coenzymes NAD,CoA, TPP,lipoic acid,FAD) (Maple syrup urine disease)**
- **Dehydrogenation (FAD)**

- **End products**:
- 1.The catabolism of **isoleucine** ultimately yields acetyl CoA and succinyl CoA, rendering it both ketogenic and glucogenic.
- 2. **Valine** yields succinyl CoA and is glucogenic.
- 3. **Leucine** is ketogenic, being metabolized to acetoacetate and acetyl CoA.

Biosynthesis of nonessential amino acids

- Nonessential amino acids are synthesized from **intermediates of metabolism**

- or, as in the case of tyrosine and cysteine, from the **essential amino acids** phenylalanine and methionine, respectively

Synthesis from α-keto acids (Transamination)

- **Alanine, aspartate, and glutamate** are synthesized by transfer of an amino group to the α-keto acids

pyruvate, oxaloacetate, and α-ketoglutarate, respectively.

These are **transamination** reactions

- **Glutamate** is unusual in that it can also be synthesized by the reverse of **oxidative deamination, catalyzed by glutamate dehydrogenase**

Synthesis by amidation

- **Glutamine**: This amino acid, which contains an amide linkage with ammonia at the γ-carboxyl, is formed from glutamate by----**glutamine synthetase & breakdown by glutaminase**

- ATP requiring

- In addition to producing glutamine for protein synthesis, the reaction also serves as a major mechanism for the detoxification of ammonia in brain and liver

- **Asparagine**: This amino acid, which contains an amide linkage with ammonia at the β-carboxyl, is formed from **aspartate** by **asparagine synthetase**, using glutamine as the amide donor
- Breakdown by **asparaginase** into aspartate and ammonia.

Asparagine: – (leukemic cells)

Aspartate :–

- By transamination forms OAA
- With citrulline forms argininosuccic acid in urea cycle
- Acts an excitatory neurotransmitter in CNS
- Takes part in purines and pyrimidines synthesis

GLUTAMIC ACID (Glutamine)

(physiological functions)

- Glutathione formation (RBCs, gammaglutamyl cycle)
- GABA inhibitory neurotransmitter(formed by decarboxylation)
- Glutamine (provides ammonia in the distal convoluted tubules)
- α-ketogluatrate (enters citric acid cycle)

- Acts as carrier of ammonia from most tissues to liver
- Gives up ammonia to form urea
- In brain prevents the accumulation of ammonia
- In the synthesis of purines
- Formation of GMP from xanthylate (XMP)

Tyrosine

- Tyrosine is formed from phenylalanine by **phenylalanine hydroxylase**.
- The reaction requires molecular oxygen and the coenzyme **tetrahydrobiopterin (BH_4)**
- One atom of molecular oxygen becomes the hydroxyl group of tyrosine, and the other atom is reduced to water. During the reaction, tetrahydrobiopterin is oxidized to dihydrobiopterin.

- Tetrahydrobiopterin is regenerated from dihydrobiopterin in a separate reaction requiring NADH by **dihydropteridine reductase**

- Tyrosine is formed from an essential amino acid and is, therefore, nonessential only in the presence of adequate dietary phenylalanine

PHENYLALANINE & TYROSINE (physiological functions)

- Catecholamines formation
- Thyroid hormones formation
- Melanin formation

Catecholamines

- **Dopamine, norepinephrine, and epinephrine** are biologically active (biogenic) amines that are collectively termed catecholamines.

- Dopamine and norepinephrine function as **neurotransmitters in the brain and the autonomic nervous system.**

- Norepinephrine and epinephrine are also synthesized in the **adrenal medulla**.

Function:

- Outside the nervous system, norepinephrine and its methylated derivative, epinephrine, act as regulators of carbohydrate and lipid metabolism.

- Norepinephrine and epinephrine are released from storage vesicles in the adrenal medulla in response to fright, exercise, cold, and low levels of blood glucose.

- They increase the degradation of glycogen and triacylglycerol, as well as increase blood pressure and the output of the heart.

- These effects are part of a coordinated response to prepare the individual for emergencies, and are often called the “fight-or-flight” reactions

Synthesis of catecholamines

- The catecholamines are synthesized from **tyrosine**
- Tyrosine is first hydroxylated by **tyrosine hydroxylase** to form 3,4-dihydroxyphenylalanine (DOPA)
- The tetrahydrobiopterin-requiring enzyme is abundant in the central nervous system, the sympathetic ganglia, and the adrenal medulla, and is the rate-limiting step of the pathway

- DOPA is decarboxylated (**decarboxylase**) in a reaction requiring pyridoxal phosphate to form **dopamine**

- which is hydroxylated by the copper-containing **dopamine β-hydroxylase** to yield **norepinephrine.**

- **Epinephrine** is formed from norepinephrine by **an N-methylation reaction using S-adenosylmethionine** as the methyl donor

- In **Parkinson disease --- deficiency of neurotransmitter DOPAMINE**
- **Treatment includes giving L-DOPA**

Degradation of catecholamines:

- The catecholamines are inactivated **by oxidative deamination catalyzed by monoamine oxidase (MAO)**, and

- by **O-methylation carried out by catechol-O-methyltransferase**

- The two reactions can occur in either order.

- The metabolic products of these reactions are excreted in the urine as **vanillylmandelic acid** from epinephrine and norepinephrine, and **homovanillic acid** from dopamine

MAO inhibitors

- MAO is found in neural and other tissues, such as the gut and liver.

- In the neuron, this enzyme functions as a “safety valve” to oxidatively deaminate and inactivate any excess neurotransmitter molecules (norepinephrine, dopamine, or serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

- The MAO inhibitors may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation

- This causes activation of norepinephrine and serotonin receptors, and may be responsible for the antidepressant action of these drugs

- **Parkinson disease**, a neurodegenerative movement disorder, is due to insufficient **dopamine** production as a result of the idiopathic loss of dopamine-producing cells in the brain.

- Administration of **L-DOPA** (**levodopa**) is the most common treatment.

MELANIN

- Formed from phenylalanine and tyrosine
- Chief pigment of skin
- Also present eyes and brain (substantia nigra)
- Produced by specialized cells called melanocytes