

Metabolism of aminoacids

Glycine

- Simple, Optically inactive
- Non essential AA
- Glucogenic

Synthesis of Glycine

- From serine
- From threonine
- From CO_2 , NH_3 and 1-c unit(methylene)
- From glyoxylate
- From choline

From serine

Catalysed by serine hydroxy methyl transferase

Serine Glycine

From Threonine

Catalysed by Threonine aldolase

Threonine Glycine

Acetaldehyde

+

Denovo synthesis of glycine

From CO_2 , NH_3 and 1-C unit

Enzyme-Glycine synthase

Reverasal of glycine cleavage system

$\text{NH}_3 + \text{CO}_2$ Glycine

From glyoxylate

Glycine amino transferase can catalyze the synthesis of glycine from glyoxylate (Transamination)

From choline

Choline Betaine Dimethyl glycine

Sarcosine

Glycine

Catabolism of glycine

- ☐ Glycine cleavage system
- ☐ Glucogenic pathway

Glycine cleavage system

Multienzyme complex

Enzymes- Glycine decarboxylase

Aminomethyl transferase

Methylene THFA synthase

Lipoamide dehydrogenase

Coenzymes- NAD,PLP,Lipoamide,THFA

Catalyse oxidative deamination of glycine to form NH_3 , CO_2 and 1-C unit

Reversal of glycine synthase

Glucogenic pathway

Glycine enters into the glucogenic pathway by getting first converted to serine

The serine is then converted to pyruvate by serine dehydratase

Conversion of glycine to special products

- ☐ Synthesis of proteins (about 30% of collagen is glycine)
- ☐ Synthesis of heme
- ☐ Synthesis of glutathione (gamma glutamyl cysteinyl glycine)
- ☐ Synthesis of purine ring:- C_4 , C_5 and N_7 of purines are derived from glycine
- ☐ Conjugation reactions

Formation of bile salt:-Glycine conjugate with primary bile acids(Cholic acid,chenodeoxy cholic acid) to form bile salt

Eg.Glycocholic acid, glycochenodeoxy cholic acid

Detoxification of drugs/toxins

Eg.Glycine + Benzoic acid Hippuric acid

- ☐ Glycine as a neurotransmitter
- ☐ Synthesis of creatine(Gly+ Arg + Met)

Defects associated with Glycine metabolism

1. Nonketotic hyperglycinemia(NKH)

Due to defect in glycine cleavage system

Gly level increased in blood,urine and CSF

Clinical features

Mental retardation,seizures

2. Primary hyperoxaluria

Protein targetting defect

Glyoxylate aminotransferase is normally present in peroxisome

But in this condition it goes to MC and becomes inactive

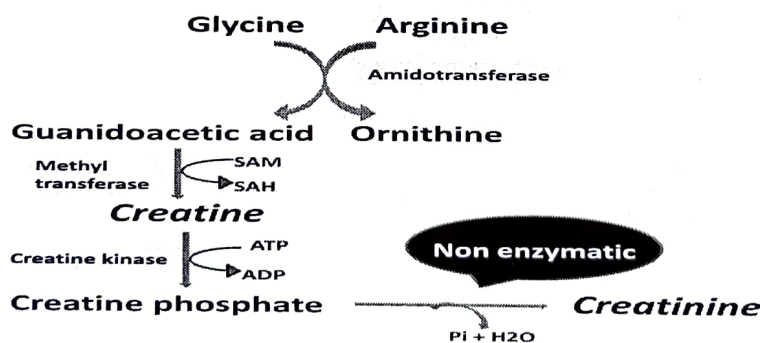
So excess glyoxylate is converted to oxalates

Result in nephrolithiasis and hematuria

Synthesis of creatine

Synthesis of Creatine

Synthesized from 3 AAs- Gly,Arg,Met



- The first reaction occurs in the mitochondria of kidney and pancreas
- It involves the transfer of guanidino group of arginine to glycine, catalysed by glycine - arginine amidotransferase to produce guanidoacetate
- S-Adenosylmethionine (active methionine) donates methyl group to guanidoacetate to produce creatine (Transmethylation)
- This reaction occurs in liver
- Creatine is reversibly phosphorylated by creatine kinase to form creatine phosphate
- Serves as an immediate store of energy in the muscle
- During muscle contraction,energy is derived from ATP hydrolysis
- The ATP is regenerated by the hydrolysis of Creatine phosphate:-Lohmann's reaction
- The creatine phosphate may be converted to its anhydride, creatinine.

- Creatinine is excreted in urine.
- It is a non-enzymatic spontaneous reaction

Clinical significance

In muscular dystrophies, blood creatine level is increased

Serum creatine level: 0.2 - 0.4 mg/dl

Creatinine level in blood is a sensitive indicator of renal function.

Normal serum creatinine level: 0.7 - 1.4 mg/dl.

The enzyme CK is elevated in MI.

Metabolism of aromatic amino acids

Phenyl alanine

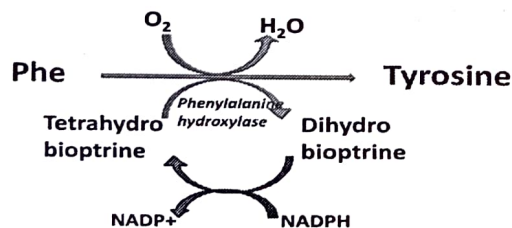
- Essential
- Partly glucogenic and partly ketogenic
- Converted to tyrosine

Conversion of phenyl alanine to Tyrosine

Phe is hydroxylated to form Tyr

Catalysed by Phenylalanine hydroxylase

Coenzymes-NADPH,NADH and tetrahydrobiopterine



Tyrosine

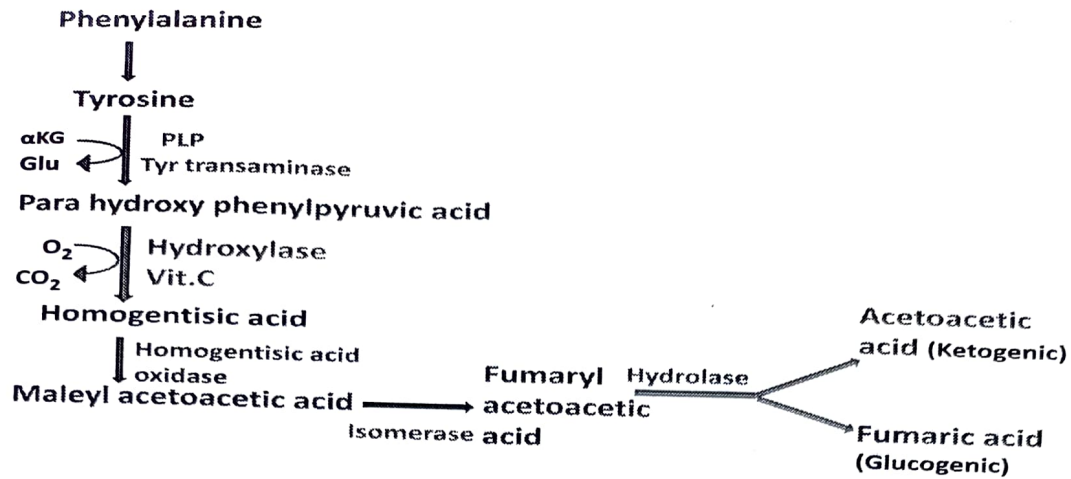
Synthesized from Phe

Non essential

Partly glucogenic and partly ketogenic

Sparing action of Tyr on Phe - If adequate Tyr is supplied in food, the need for phe is minimal

Catabolism of tyrosine (Phenylalanine)



Important products formed from tyrosine

- Melanin
- Catecholamines (Epinephrine, nor epinephrine, Dopamine)
- Thyroid hormones (T₃, T₄)

Synthesis of melanin

Pigment gives black colour to skin and hair

Tyrosinase is the only enzyme involved in synthesis-catalyse first two reactions

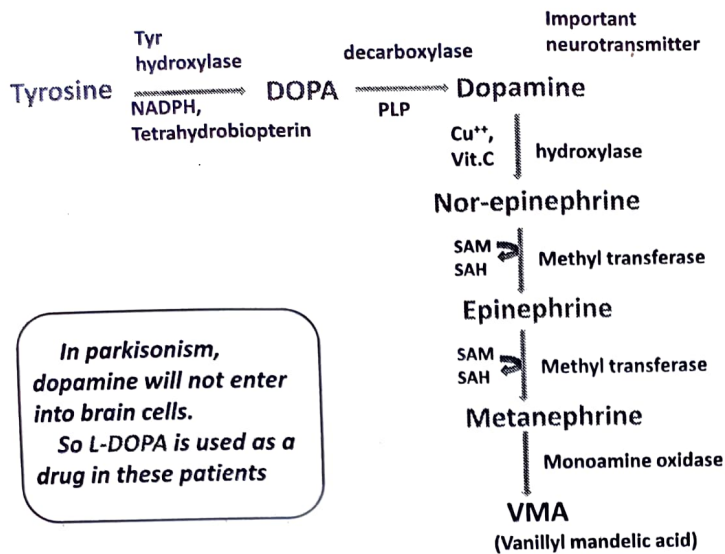
Remaining reactions are non enzymatic

Tyrosinase- Cu⁺⁺ containing mono-oxygenase

Synthesis of catecholamines

Presence of catechol nucleus

Include epinephrine (adrenalin), nor-epinephrine, dopamine



Physiological actions of epinephrine

Increase BP

Increase the rate and force of myocardial contraction

Relaxation of smooth muscles of bronchi

Anti insulin in nature

Alpha methylDOPA-an antihypertensive drug It inhibit DOPA decarboxylase inhibit epinephrine production

Clinical significance of VMA

Excreted in urine

Normal daily excretion= 2-6mg/day

Level increased in tumours of medulla

- pheochromocytoma
- neuroblastoma

Synthesis of thyroid hormones(T₃,T₄)

Tyrosine iodinated to form monoiodotyrosine(MIT) and diiodotyrosine(DIT)

Phenylketonuria(PKU)

5 types described

Type 1(Classical PKU) is due to phenyl alanine hydroxylase deficiency

Other types- due to defect in synthesis of biopterin

Biochemical abnormalities

Increased level of Phenylalanine

Decreased level of tyrosine

Excess Phe is channeled to an alternate pathway for the production of phenylketone (Phenylpyruvate) phenyl acetate, phenyl lactate, excreted in urine

Clinical features

- Mental retardation with low IQ
- Agitation, hyperactivity, convulsions - due to defect in neurotransmitter synthesis
- Hypopigmentation - due to inhibition of tyrosinase
- Mousy body odour - due to the presence of phenyl acetate

Lab investigations

1) Blood Phe : Normal level is 1mg/dl, but the level will be >20mg/dl in PKU

Detected by chromatography

Tandem mass spectroscopy - reliable test

2) Guthrie test

Certain strains of *Bacillus subtilis* need Phe for its growth

Bacteria can't grow in a medium devoid of Phe

Bacterial growth is proportional to Phe content in patient's blood

3) Ferric chloride test

Phe is detected by adding a drop of FeCl_3 to the urine

Blue-green colour is obtained in the positive test

4) DNA probes

Treatment

- Diet containing low Phe
- Food based on tapioca have low Phe content
- Tyrosine supplementation
- Life long treatment should be necessary

Alkaptonuria

- Due to the deficiency of homogentisate oxidase
- Include in Garrod's tetrad
- Result in excretion of homogentisic acid in urine
- Excess homogentisic acid is converted to black colour alkapton bodies
- So urine becomes black colour on standing

- By 3rd and 4th decade of life, alkapton bodies deposit in intervertebral disc, cartilages of nose, pinna of ear - Ochronosis

Clinical features

Blackening of urine

Arthritis - Alkapton bodies are deposited in joint cavities

Diagnosis

Urine becomes black on standing when it becomes alkaline

FeCl₃ test

Benedict's test - Homogentisic acid is a non carbohydrate reducing substance

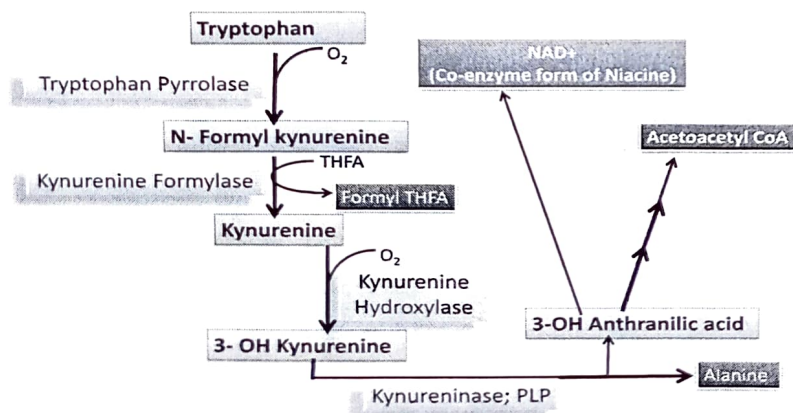
Treatment

Restrict protein intake with phe and tyrosine

Tryptophan Metabolism

Important products formed from Tryptophan

- 1) Alanine
- 2) Acetoacetyl coA
- 3) Serotonin
- 4) Melatonin
- 5) 5-HIAA
- 6) Indican

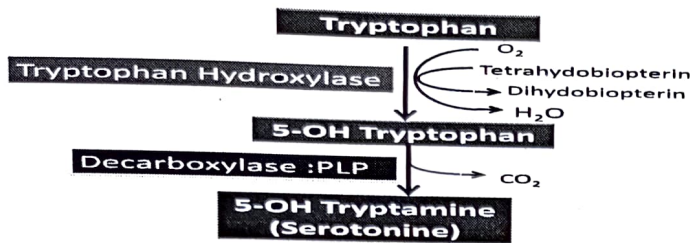


SYNTHESIS OF NIACIN FROM TRYPTOPHAN

- *QPRT – Quinolinate phosphoribosyl transferase is the rate limiting enzyme.*

About 60 mg of tryptophan forms 1 mg of niacin

Synthesis of serotonin from tryptophan



Functions

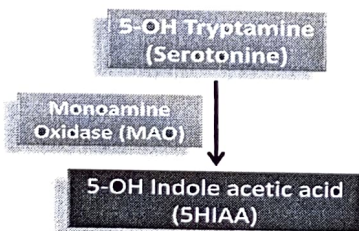
- Neurotransmitter : Regulation of cerebral activity (Stimulate), Controls the behavioral pattern, sleep, blood pressure and body temperature
- Evokes release of peptide hormones from GIT: Increases gastric motility
- Powerful vasoconstrictor – smooth muscle constriction in bronchioles and arterioles
- Sensitivity to pain is reduced

Carbohydrate rich diet induce sleep than proten diet.Why?

When protein rich diet taken – all amino acids are available in blood

- When protein rich diet taken – all amino acids are available in blood
- Cause traffic jam in the amino acid transport system in brain
- SO, Tryptophan bulkiest amino acid - taken very slowly
- When carbohydrate rich diet is taken – insulin secretion is increased
- Lower the amino acid concentration in the blood
- Tryptophan easily enters the brain – serotonin production increased – induce sleep

Clinical significance of 5-HIAA ?



- Normal excretion of 5-HIAA is 2 – 7 mg/day

- If urine level is > 25 mg/ day diagnosis of carcinoid tumor(Argentaffinomas)
- In metastatic carcinoid tumor - up to 350mg/day
- Hartnup's Disease
- Impaired transport of tryptophan and neutral amino acids in intestine, renal tubules
- Mental retardation
- Intermittent cerebellar ataxia
- Pellegra like skin rashes
- Decreased synthesis of serotonin and niacin are responsible for neurological symptoms and pellagra like rash

• Diagnosis is by Obermeyer test

• Patients improve on a high protein diet with supplementation of niacin

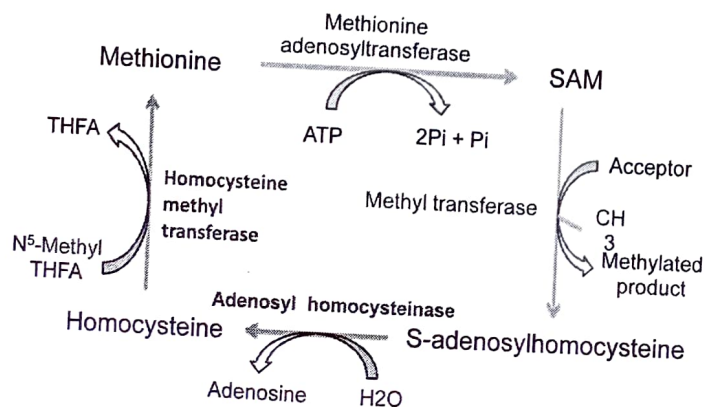
Sulfur containing amino acids

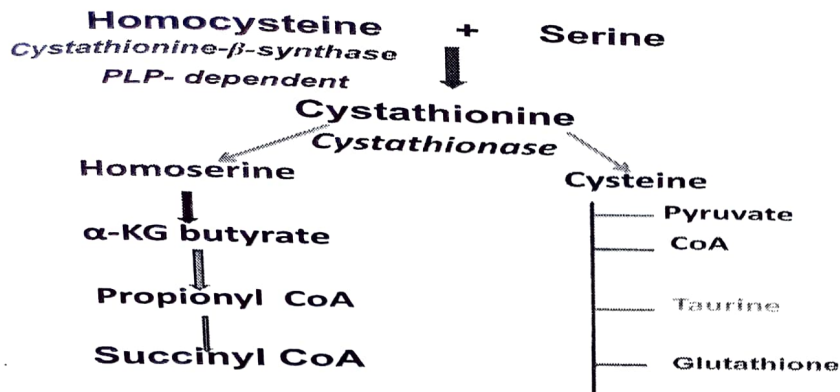
Methionine, Cysteine & Cystine

Methionine is glucogenic & essential amino acid.

Metabolism of Methionine

- Activation of methionine
- Transmethylation reactions.
- Conversion of SAM to homocysteine
- Regeneration of methionine
- Trans sulfuration





Synthesis of S-adenosylmethionine

- The synthesis of SAM occurs by the transfer of adenosyl group from ATP to sulfur atom of methionine.
- This reaction is catalysed by Methionine S-adenosyltransferase (MAT).

Transmethylation

- The transfer of methyl group (-CH₃) from active methionine to an acceptor is known as transmethylation.
- Here SAM is converted to SAH. enzyme is methyl transferase

Conversion of SAH to Hcy

- Adenosine is removed from SAH and is convert to Hcy, Catalysed by adenosyl homocysteinase

Regeneration of Met

- Homocysteine can be remethylated to methionine by N⁵-methyl tetrahydrofolate.
- This methyl group is donated from one-carbon pool, with the help of vitamin B12.

Homocysteine degradation: (trans sulfuration)

- Homocysteine condenses with serine to form cystathionine.
- This is catalysed by PLP dependent cystathionine-β-synthase.
- Absence of this enzyme leads to homocystinuria.
- Cystathionine is then hydrolyzed by cystathionase to form cysteine and homoserine
- So, -SH gp from Met is transferred to serine to form Cysteine(trans sulfuration)

Metabolic functions of Cysteine

1) Cys is oxidised to cysteic acid and then decarboxylated to taurine

- Taurine is used for conjugation of bile acids

- It is a modulator of Ca fluxes, Ca binding
- Inhibitory neurotransmitter
- Imp for the development of CVS, skeletal system, eyes, CNS

2) Cysteine is required for glutathione

Inborn errors of Sulfur containing AA metabolism

1. Cystinuria: due to transporter defect

2. Cystinosis: Cellular transport defect

- Cystine crystals deposited on lysosomes, Liver, spleen, bone marrow affected

3. Homocystinuria

Homocystinuria

Autosomal recessive

- Incidence is 1 in 2 lakhs birth
- Normal level in blood is 5-15 micromol/L
- In diseases, increases 50 – 100 times

Congenital Homocystinuria

- Autosomal recessive inherited disorder
- Approximately 40% of affected patients respond to high doses of vitamin B6
- ELEVATION of homocysteine and methionine in plasma
- Urinary excretion of homocystine is more than 300mg/day
- Clinical features
- Infants with this disorder are normal at birth.
- Clinical manifestations during infancy are nonspecific and may include:
- Mental retardation

The diagnosis is usually made after 3 yr of age, when subluxation of the ocular lens (ectopia lentis) and glaucoma occurs

- Skeletal deformities are also seen
- CHARLEY CHAPLIN GAIT

Flat foot (common)

Acquired homocystinuria

- Causes:

- a) Nutritional deficiency of vitamins B₁₂, B₆ and folic acid
- b) Metabolic:- Chronic renal diseases, hypothyroidism
- c) Drug induced:- Folate antagonists, Vit B₁₂, B₆ antagonists etc

In acquired, chances of IHD (Ischemic heart disease) & CVA (Cardiac vascular accidents) are high

Homocysteine activates Hageman's factor.

This leads to increased platelet adhesiveness and life-threatening intra vascular thrombosis

Test: Cyanide-Nitroprusside test

Treatment

- Diet low in Met and rich in Cys to be given
- In acquired, vitamin supplementation can be given

Glutamine

- Synthesised from glutamic acid

■ FUNCTIONS

- Protein synthesis
- Glucogenic amino acid
- Fixation of NH_3 in brain & intestine
- Role in maintenance of acid base balance
- Source of nitrogen atoms for purine & pyrimidine nucleotide synthesis
- Conjugating agent: eg conjugates with phenyl acetic acid to form phenyl acetyl glutamine in phenyl ketonuria.
- Synthesis of amino sugars.

Maple syrup urine disease (Branched chain ketonuria)

- Inborn error of metabolism associated with branched chain amino acids
- Incidence – 1/1 lakh births
- Deficient decarboxylation of branched chain ketoacids due to deficiency of branched chain keto acid decarboxylase enzyme
- Excretion of branched chain ketoacids & branched chain amino acids in urine
- Smell of burnt sugar or maple syrup for urine

Clinical features

- Starts in the 1st week of life
- Convulsions
- Severe mental retardation
- Acidosis
- Coma & death occurs within the 1st year of life

Tests

- Chromatography : detection of branched chain keto acids & amino acids in urine
- Dinitro-phenyl hydrazine (DNPH) test : heavy yellow precipitate
- Rothera's test : Positive

Treatment

- Diet low in branched chain amino acids

- High doses of thiamine (which is a co-factor for de-carboxylation reaction)

NITRIC OXIDE

- Important signal molecule
- Derived from arginine by the action of Nitric oxide synthase

Nitric oxide synthase

Arginine

citrulline + NO

- NO synthase is a complex enzyme employing several cofactors – NADPH, FAD, FMN, Heme & tetrahydrobiopterin.

Highly reactive free radical.

Physiological actions

1. Blood vessels : Potent vasodilator. Deficiency leads to hypertension
2. Platelets : Inhibitor of platelet aggregation
3. Intestinal system :
 - reduces gastrointestinal motility and causes relaxation of sphincters
4. CNS : implicated in the memory process.
5. Macrophages, monocytes & neutrophils : These cells produce NO, which lethally affects microorganisms.

Polyamines

- Putrescine, spermidine, spermine
- (Spermine & spermidine originally described in human semen, & hence the name)

- Aliphatic compounds having multiple amino groups.
- Synthesised from ORNITHINE & METHIONINE

Functions

- Important role in mammalian metabolism
- Necessary for cell proliferation & growth.
- Act as growth factors for cultured mammalian & bacterial cells.
- Role in stabilisation of intact cells, subcellular organelles & membranes
- Role in DNA stabilisation
- Role in protein synthesis