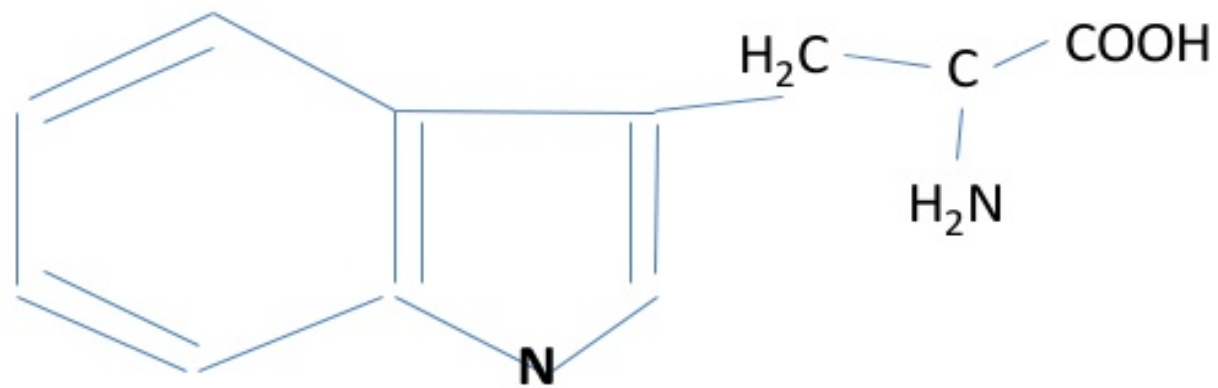


TRYPTOPHAN

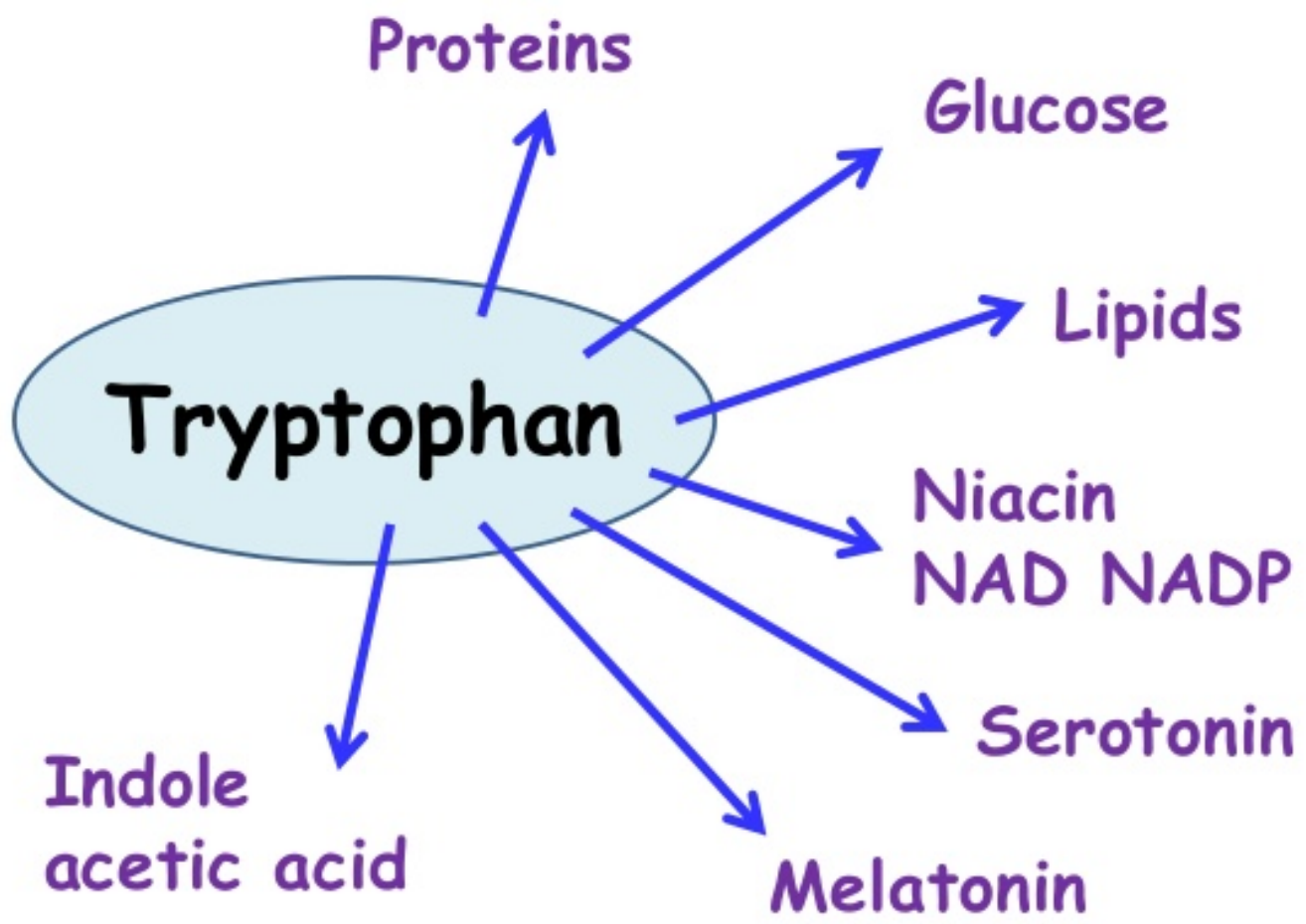
- Essential aminoacid
- Aromatic aminoacid containing indole ring.
- Both glucogenic and ketogenic
- Precursor of a neurotransmitter: **serotonin**, vitamin: **niacin** , hormone: **melatonin**.



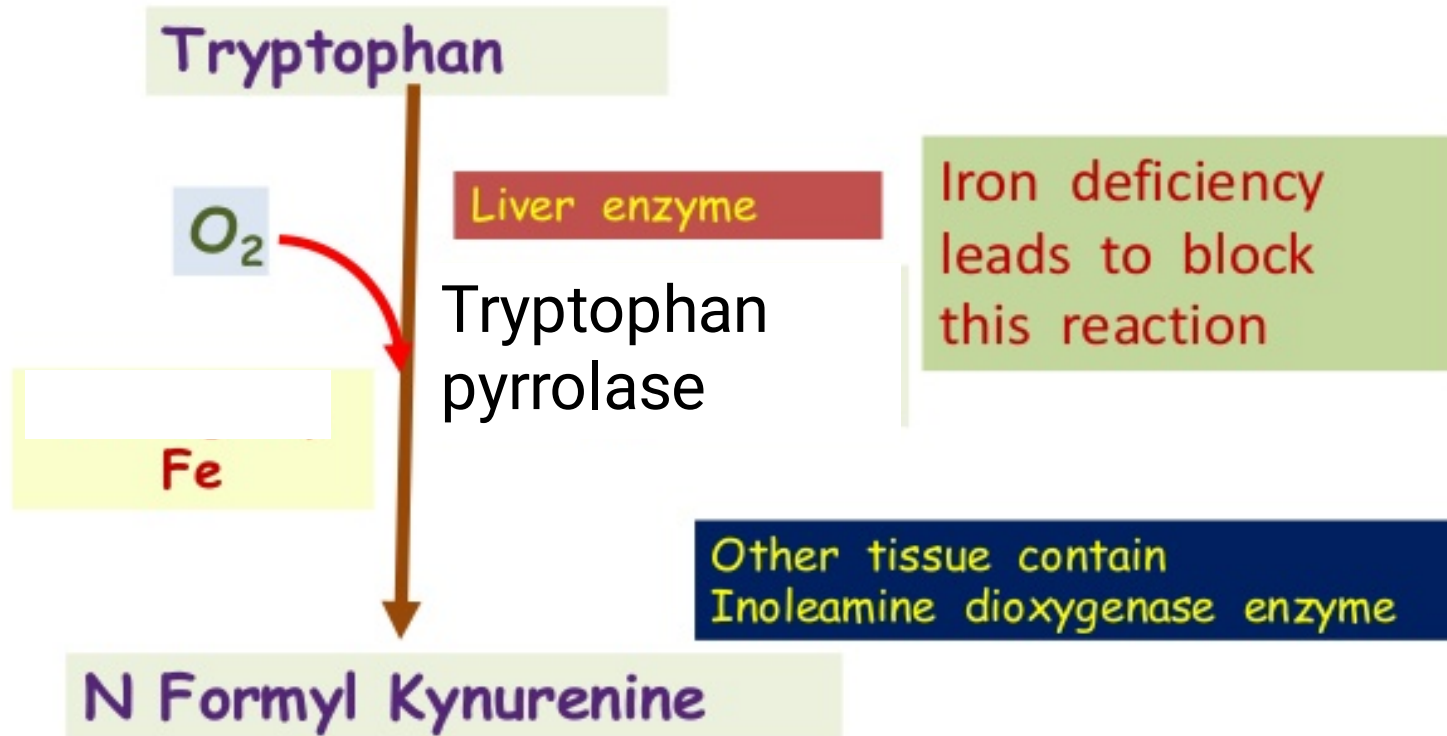


Tryptophan





Tryptophan metabolism



N Formyl Kynurenine

Tryptophan metabolism

H₂O

Kynurenine
formylase

Formate

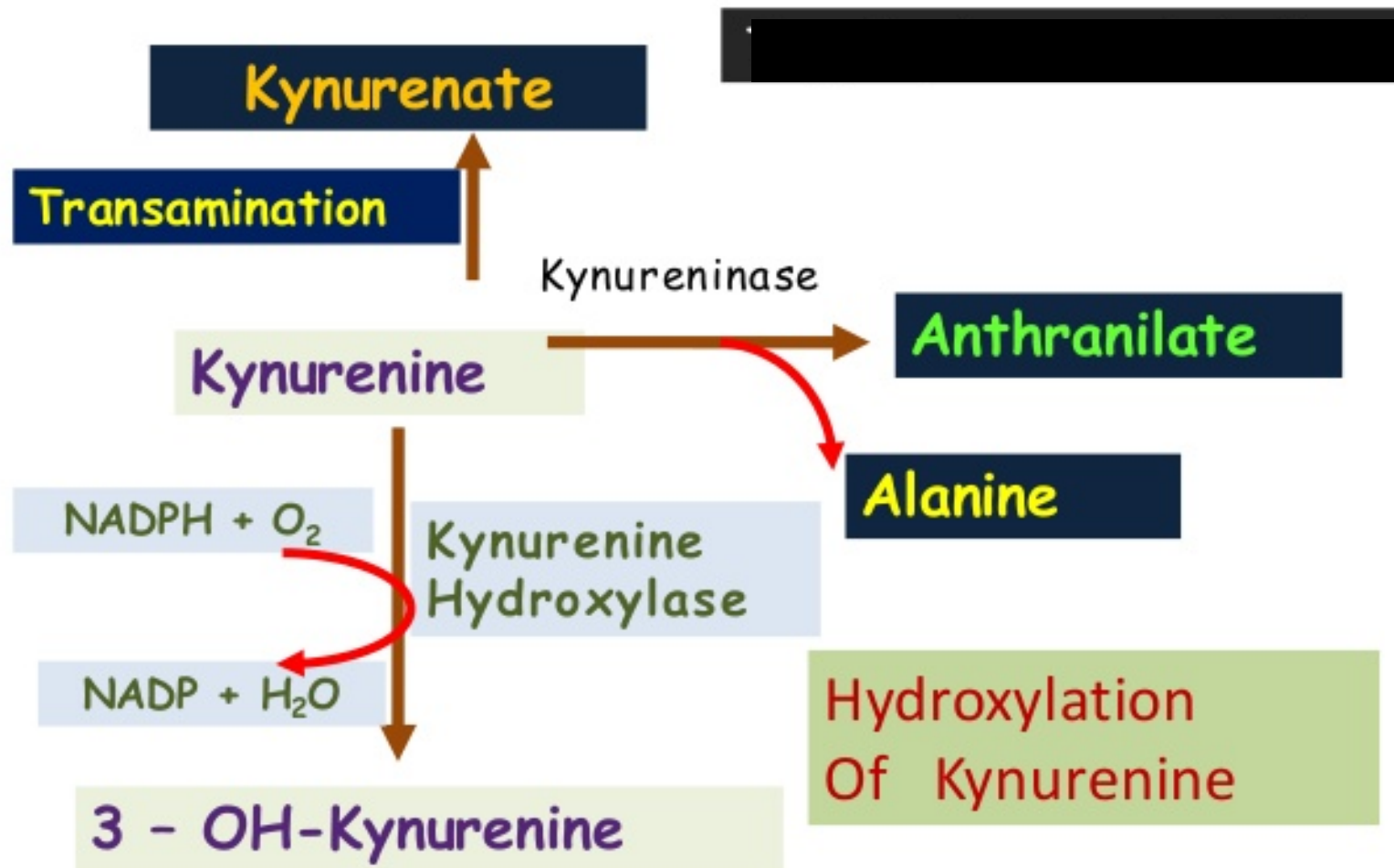
Kynurenine

enters One
'C'
Pool

After formation of
kynurenine
Pathway begins to branch

2





- **3 hydroxykynurenine will accumulate in urine in B6 deficiency.**
- **Accumulated kynurenine is shunted by transamination to xanthurenic acid.**
- **Urinary xanthurenic acid is a marker of B6 deficiency**
- **B6 deficiency can lead to pellagra**



3 -OH- Kynurenine

PLP

Kynurase

Alanine

3 - OH -anthranilic acid

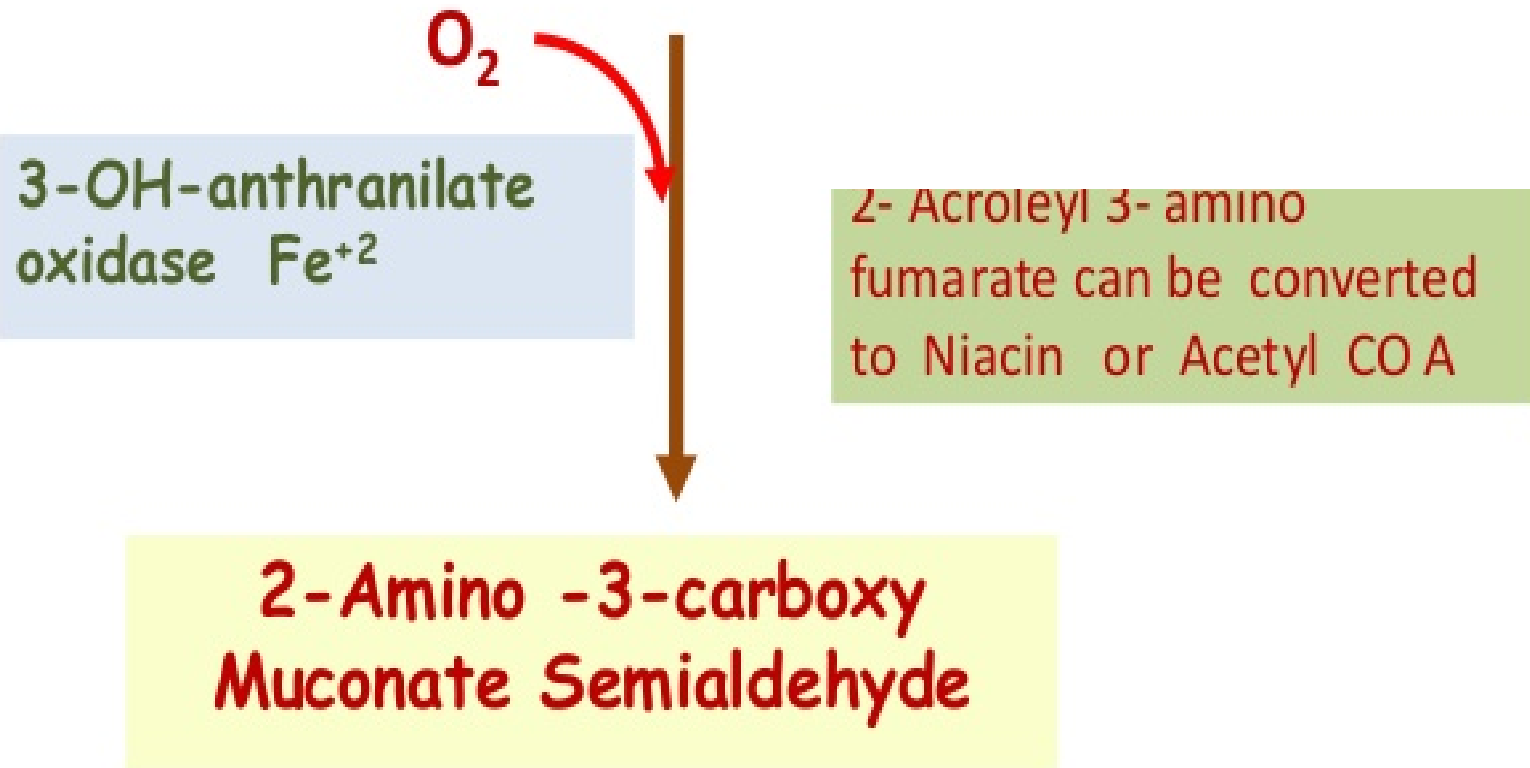
Pyruvate

Alanine so produced is
glucogenic

3



3 - OH - anthranilic acid

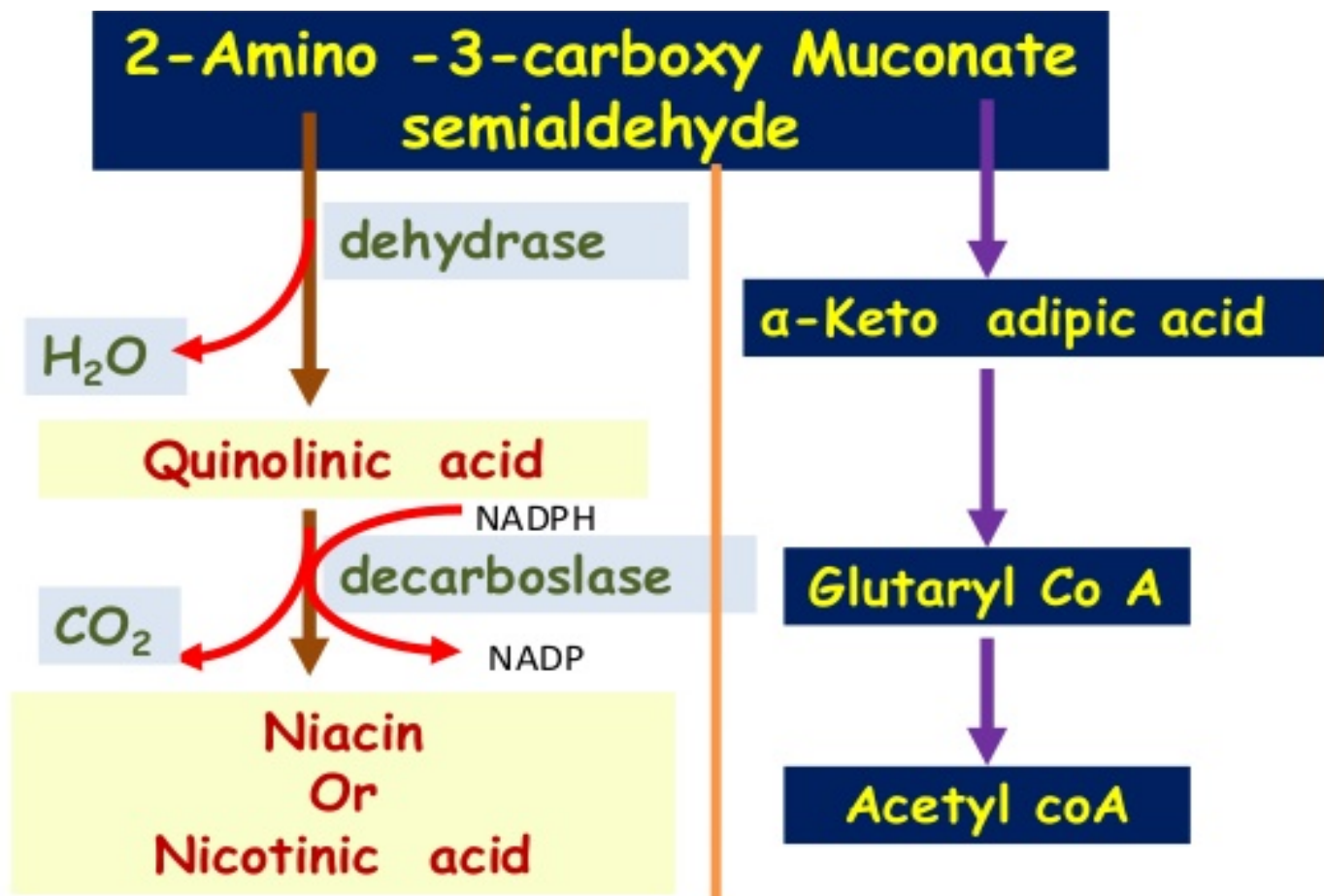


4



- **3 hydroxy-anthranilate is oxidised to amino carboxy muconic semialdehyde.**
- **This undergoes a series of reactions to form alpha ketoadipate**
- **Alpha ketoadipate finally gets converted to acetoacetate.**





60 gms tryptophan  1gm Niacin

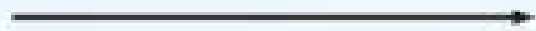
Synthesis of NAD and NADP

- 3 hydroxy anthranilate is converted to quinolinate through several steps
- Quinolinate undergoes decarboxylation and phosphoribosylation to form Nicotinate mononucleotide (NMN). PRPP is the donor of ribose 5 phosphate.
- Enzyme required Quinolinate phosphoribosyl transferase
- Rate limiting step



- **Next step: AMP is added from ATP, P_{Pi} is released.**
- **Desamido NAD is formed.**
- **Amine group is donated by glutamine to form NAD**
- **NADP is formed by further phosphorylation**
- **60 mg of tryptophan forms 1mg of niacin. This is niacin equivalent.**
- **Free niacin is not produced from tryptophan.**





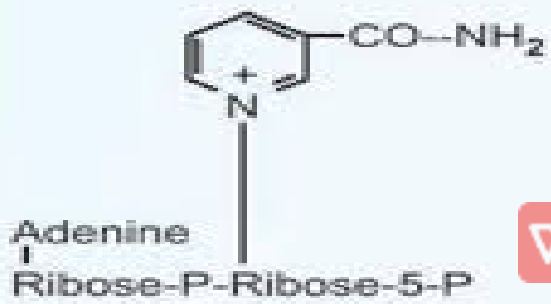
(-CO₂)



NMN (Nicotinate mononucleotide)



Desamido-NAD⁺



NAD⁺ (Nicotinamide-adenine dinucleotide)



Edit with WPS Office

Niacin

- It is synthesised as NAD or NADP from tryptophan
- It is vitamin B3.
- It acts as coenzyme for various metabolic reactions
- Deficiency of tryptophan leads to pellagra.



Pellagra

- **Definition:** It is a disease caused by deficiency of niacin. The deficiency can be due to dietary deficiency or defect in formation of niacin from tryptophan



CLINICAL FEATURES

- 04 Ds

Dermatitis

Diarrhoea

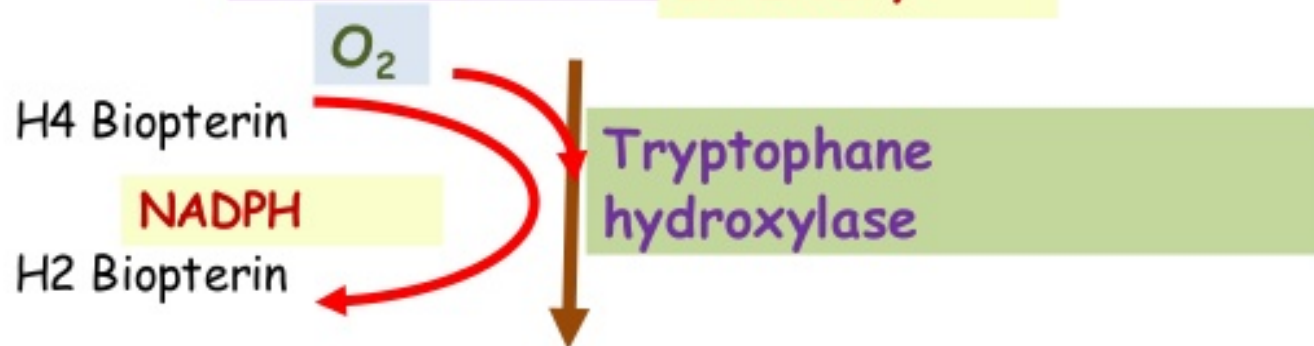
Dementia

Death

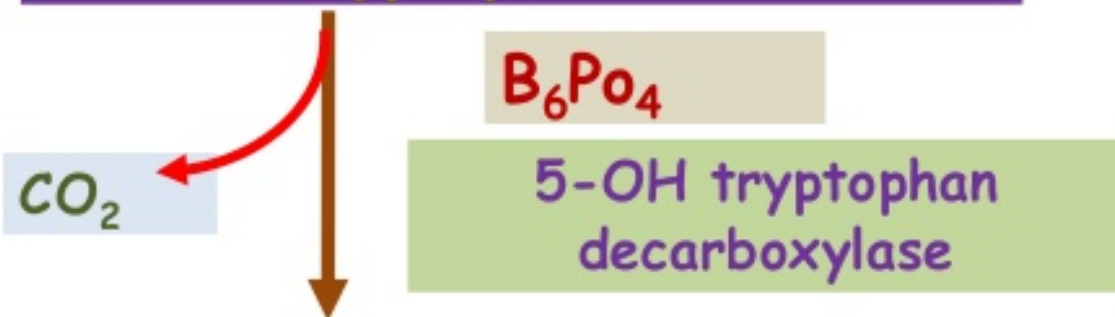


Tryptophan to serotonin

Tryptophan In Liver,



5-OH Tryptophan



5-OH tryptamine

Serotonin

serotonin

- Synthesised from tryptophan
- It is a stimulatory neurotransmitters
- It also induces sleep
- Responsible for mood elevation
- Its deficiency leads to depression



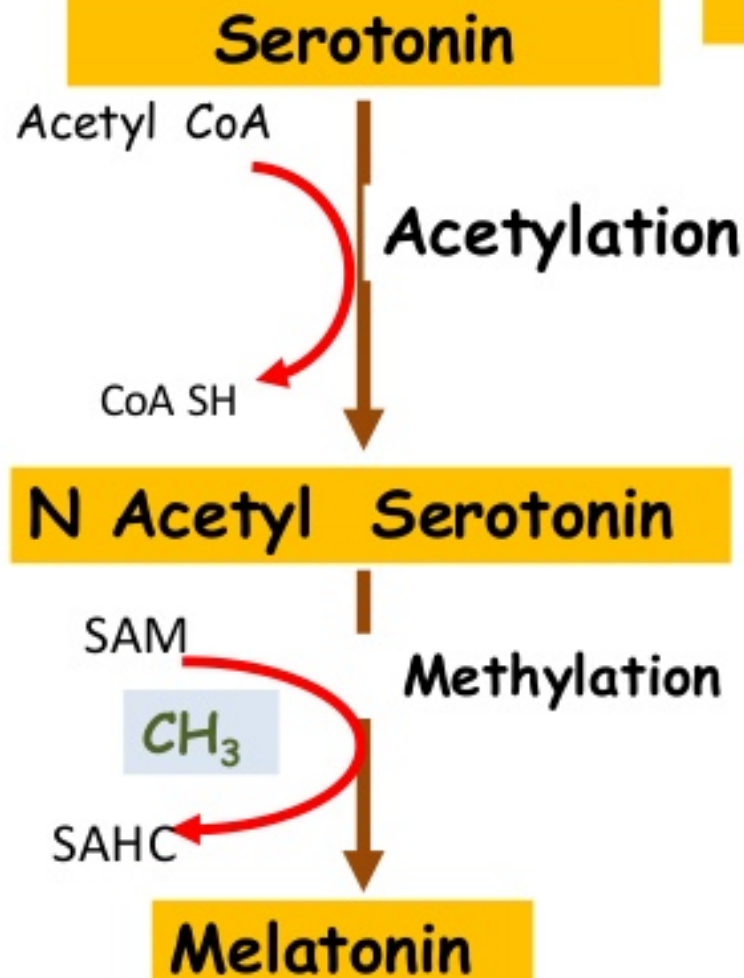
- 5 hydroxy tryptamine is **Serotonin**.
- Synthesized in gastric mucosa, Brain, Intestine.

- **Acts as**

- Neurotransmitter in brain – Stimulator,
- Deficiency leads to depression and Schizophrenia
- Causes contraction of smooth muscle of arterioles and bronchioles.
- Also induces sleep
- Responsible for mood elevation, behavior pattern.



synthesis of Melatonin



In Pineal gland

- Melatonin is Derivative of Tryptophan
- It is N- acetyl -5- methoxy tryptamine.
- It is sleep inducing molecule.
- Responsible of regulation of circadian rhythm.
- It has inhibitory effect on gonads
- Blocks action of MSH ,

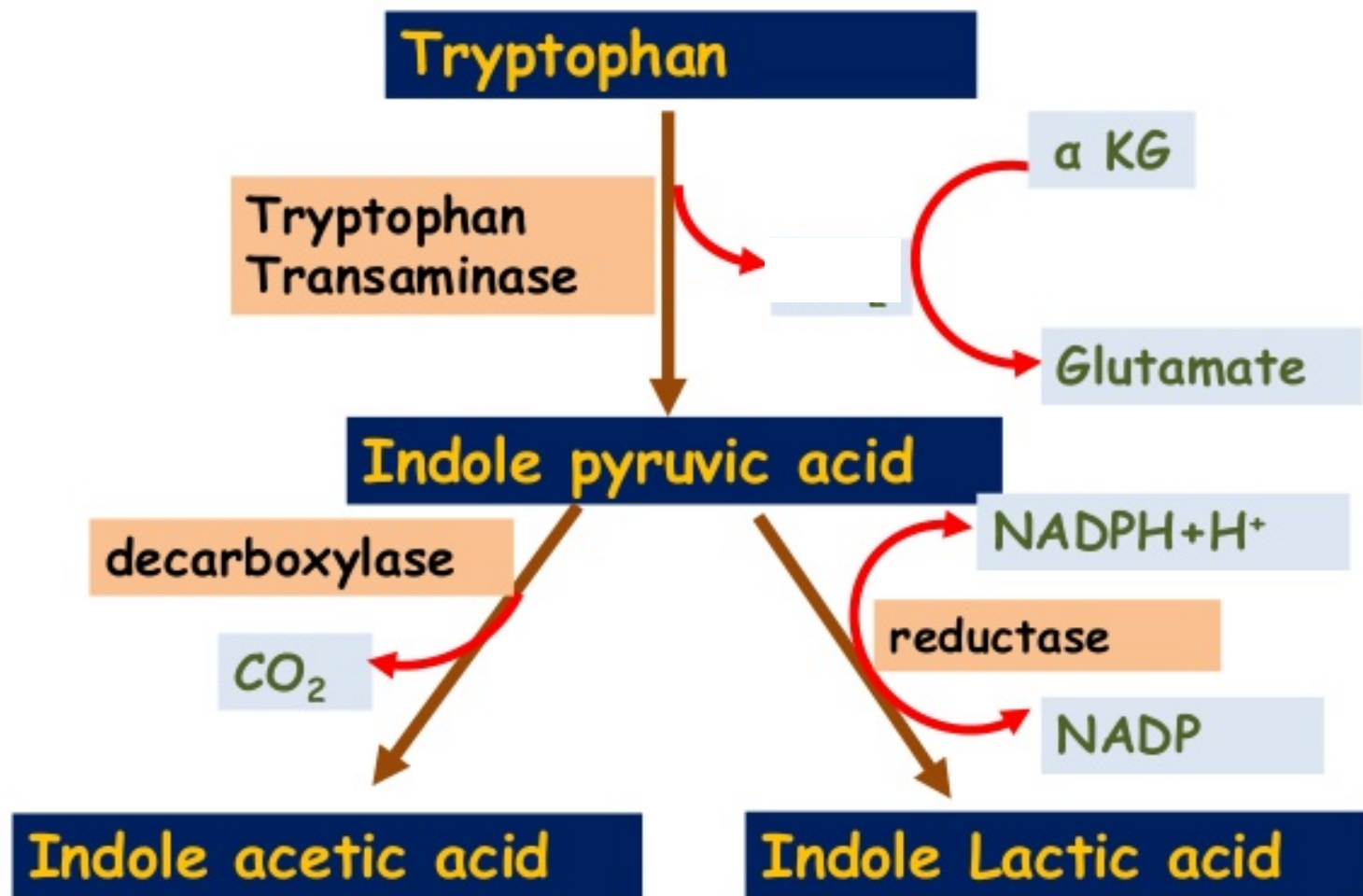
ACTH

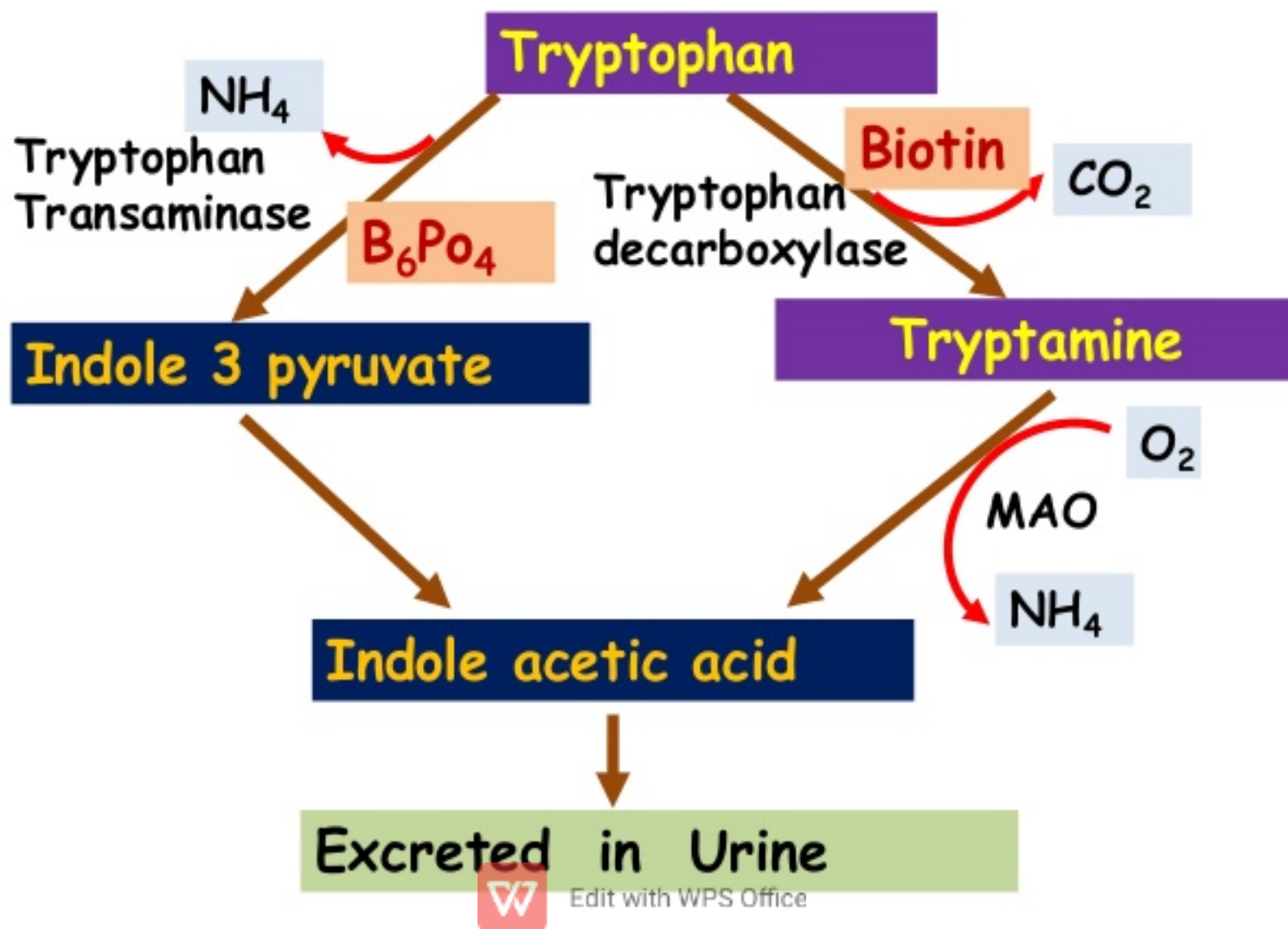


melatonin

- **Synthesised from tryptophan**
- **Secreted by pineal gland**
- **It is hormone that maintains circadian rhythm**







Hartnup's disease

- Autosomal recessive disorder
- Defect in absorption of aromatic amino acids from intestine, also reabsorption from renal tubules
- Aminoacids are excreted in urine.

- Clinical features:
 1. pellagra: due to deficiency of tryptophan
 2. Dermatitis and ataxia



- **Diagnosis:**

1. **Aminoacids are present in urine**
2. **Obermeyer test: detection of indole compounds in urine.**

- **Treatment:**

1. **high protein diet**
2. **Supplementation of niacin**
3. **Avoid exposure to sunlight**



Carcinoid syndrome

- Serotonin is produced by argentaffin cells of GIT
- Tumor of these cells (argentaffinomas) is known as carcinoid tumor
- Common site: small intestine and appendix
- Carcinoid syndrome can occur due to carcinoid tumors or in other malignancies like lung cancer

- **Clinical features: flushing, diarrhoea, bronchospasm, pain abdomen**
- **Symptoms of pellagra seen**
- **5 HIAA levels in urine >25mg/day is diagnostic of carcinoid syndrome.**
- **Treatment is removal of tumor.**

BRANCHED CHAIN AMINOACIDS

- Valine, leucine, isoleucine
- Essential amino acids
- Leucine is only ketogenic amino acid produce acetyl CoA.
- Isoleucine is both ketogenic and glucogenic
- Valine is glucogenic



- Branched chain amino acids serve as alternate fuel for brain specially during starvation



- Isoleucine produces propionyl CoA, valine produces succinyl CoA
- Catabolism: First two reactions are :Transamination and oxidative decarboxylation
- Alpha ketoacid dehydrogenase is a complex mitochondrial enzyme



- It is comparable to PDH and requires 5 coenzymes
 - TPP, Lipoamide, Coenzyme A, NAD⁺, FAD⁺
- It is a regulatory enzyme
- Ketoacids are converted to corresponding acylthioesters



Metabolism of branched chain amino acids

Valine, Leucine, Isoleucine

**Branched chain amino acid
transaminase**

Corresponding α -ketoacids

(α -ketoisovalerate, α -ketoisocaproate, α -keto β -methyl valerate)

NAD⁺, CoASH

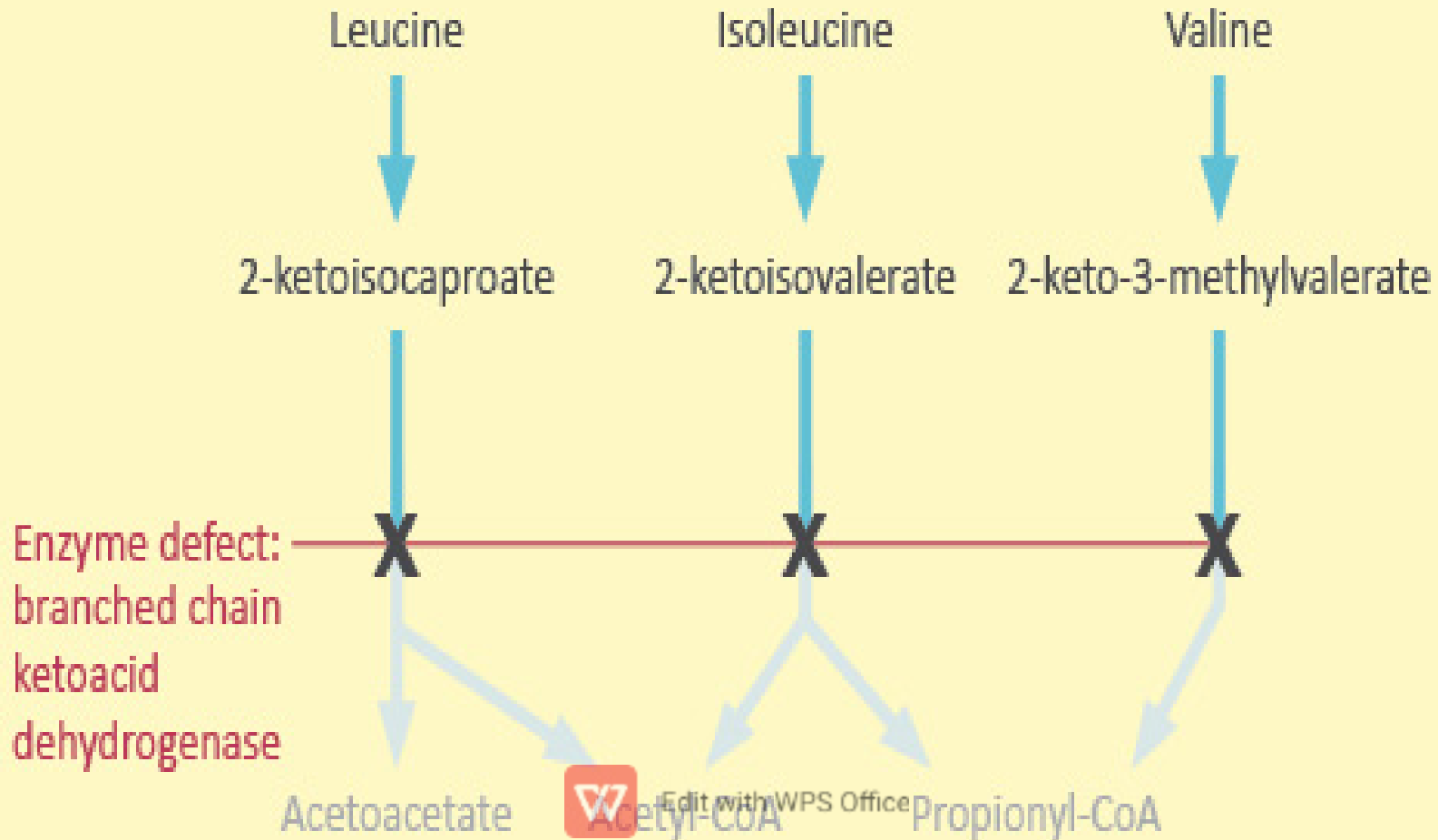
α -Ketoacid dehydrognase

NADH, CoA

Corresponding α , β -unsaturated acyl CoA thioesters
(Isobutyryl CoA, Isovaleryl CoA, α -methylbutyryl CoA)



Enzyme Defect in Maple Syrup Urine Disease (MSUD)



Maple syrup urine disease

- **Metabolic disorder of branch chain amino acid metabolism**
- **Enzyme defect: branch chain ketoacid decarboxylase.**
- **Excretion of keto acids and hydroxy acids in urine**
- **Urine has smell of burnt sugar(maple syrup)**



Biochemical complications

- ① **Accumulation of branched chain amino acids causes an impairment in transport & function of other amino acids.**
- ① **Protein biosynthesis is reduced.**
- ① **Branched chain amino acids competitively inhibit glutamate dehydrogenase.**

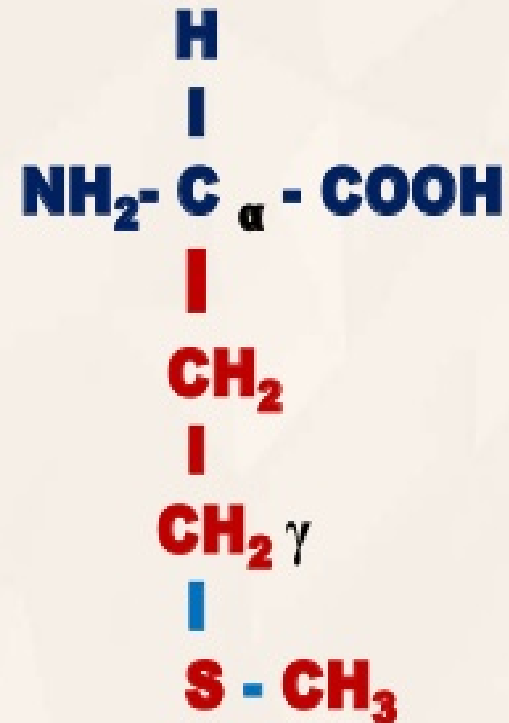
Clinical features

- **Manifests by first week of life**
- **Child is lethargic, refuses to feed and vomits**
- **Convulsions are present**
- **Death occurs in one year if untreated**



METHIONINE

- ⌘ Sulfur containing A.A.
- ⌘ Aliphatic AA.
- ⌘ Neutral AA.
- ⌘ α -amino γ thiomethyl butyric acid.
- ⌘ Essential AA.
- ⌘ Glucogenic AA.



Sulphur containing aminoacids

METHIONINE

- **Essential**
- **Glucogenic: forms succinyl CoA**
- **S-adenosyl methionine serves as methyl donor**
- **Source of cysteine in our body**



PROTEIN SYNTHESIS

- ⌘ Methionine is coded by codon **AUG**.
- ⌘ This codon is called **start codon**.
- ⌘ Methionine is first amino acid used to build a protein chain.



Metabolism of methionine

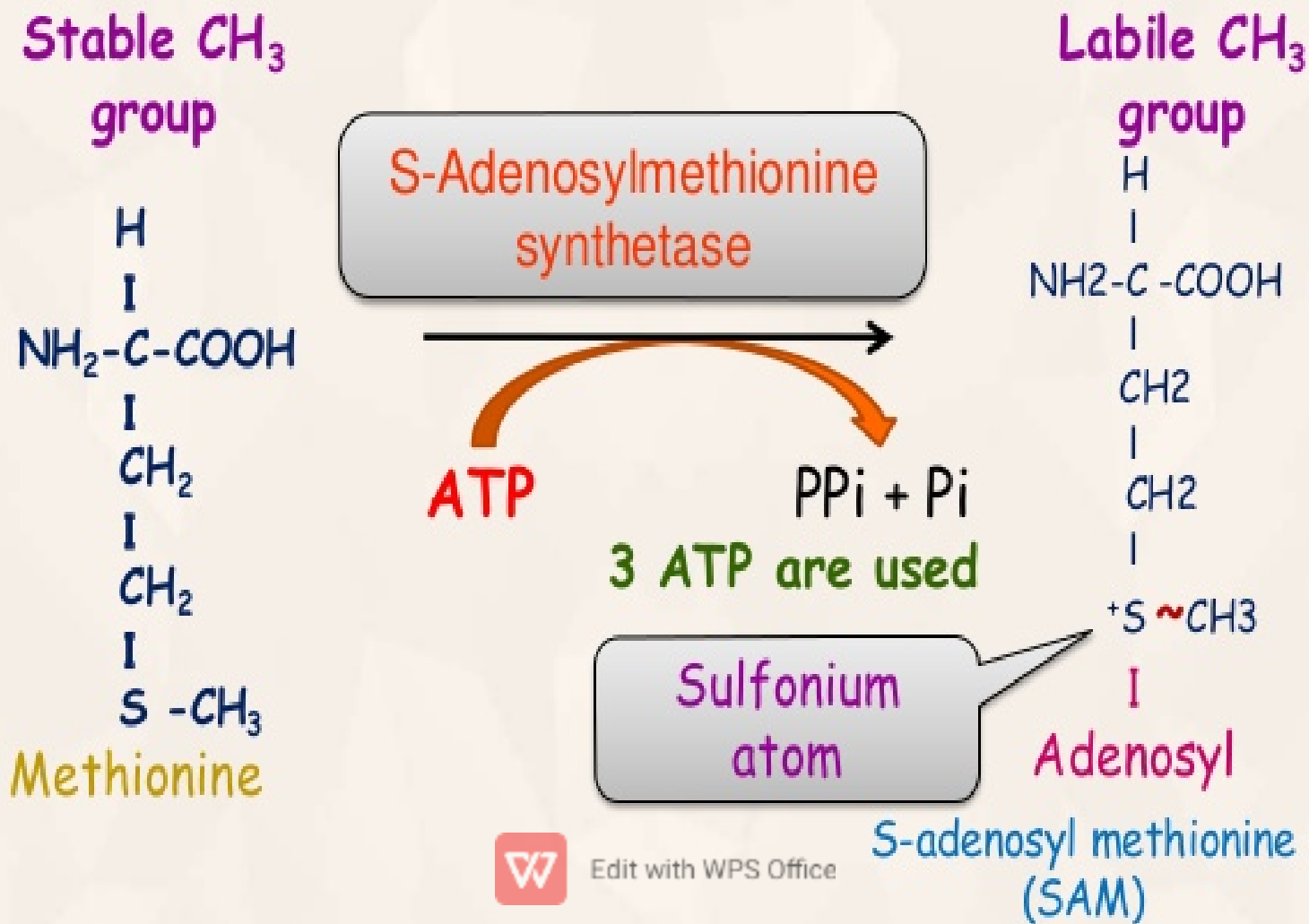
- Activation to S-adenosyl methionine: active methionine.
Adenosyl group is donated by ATP

Enzyme is methionine adenosyl transferase or SAM Synthetase

PPi and Pi are released.



Formation of Active Methionine

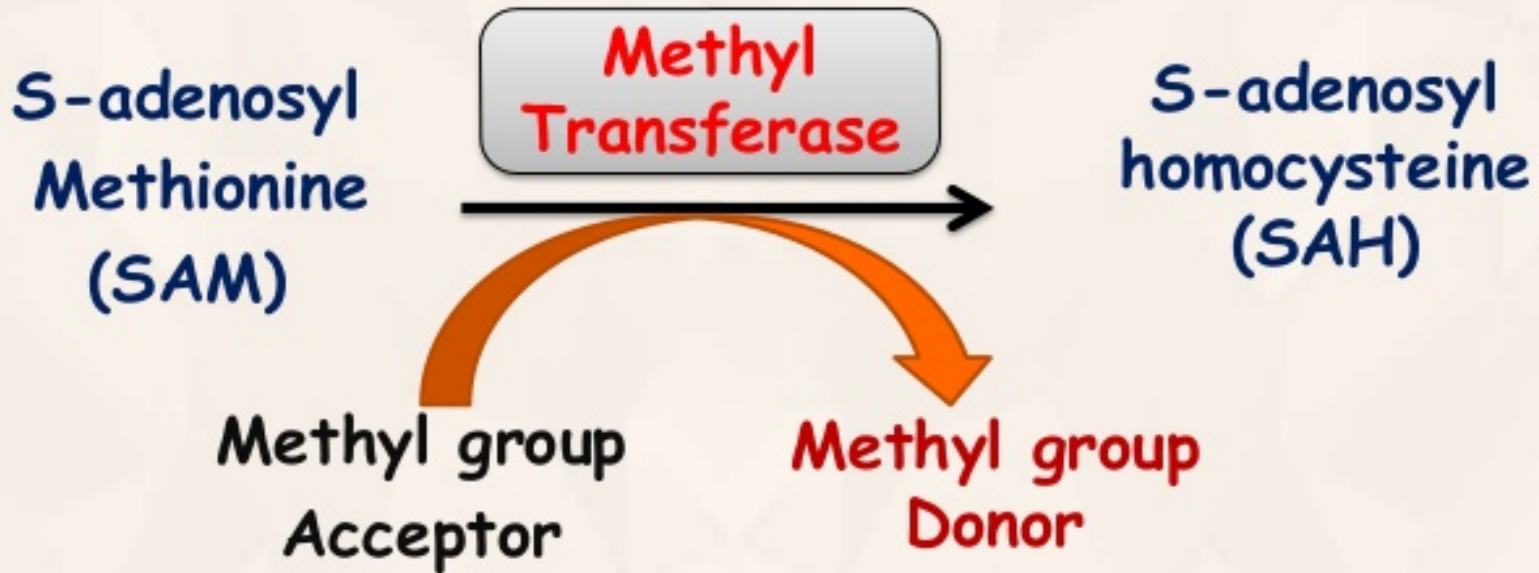


Methyl transfer

- Thioether linkage of methionine is stable but methyl group becomes labile on addition of adenosine.
- Methyl group can be donated to an acceptor :
transmethylation reaction



TRANSMETHYLATION



Transmethylation:

- transfer of methyl group from a donor to acceptor compound is termed transmethylation.
- SAM serves as the donor in transmethylation reactions
- SAM gets converted to SAH
- Loss of free energy in the reaction makes it irreversible.



Transmethylation reactions

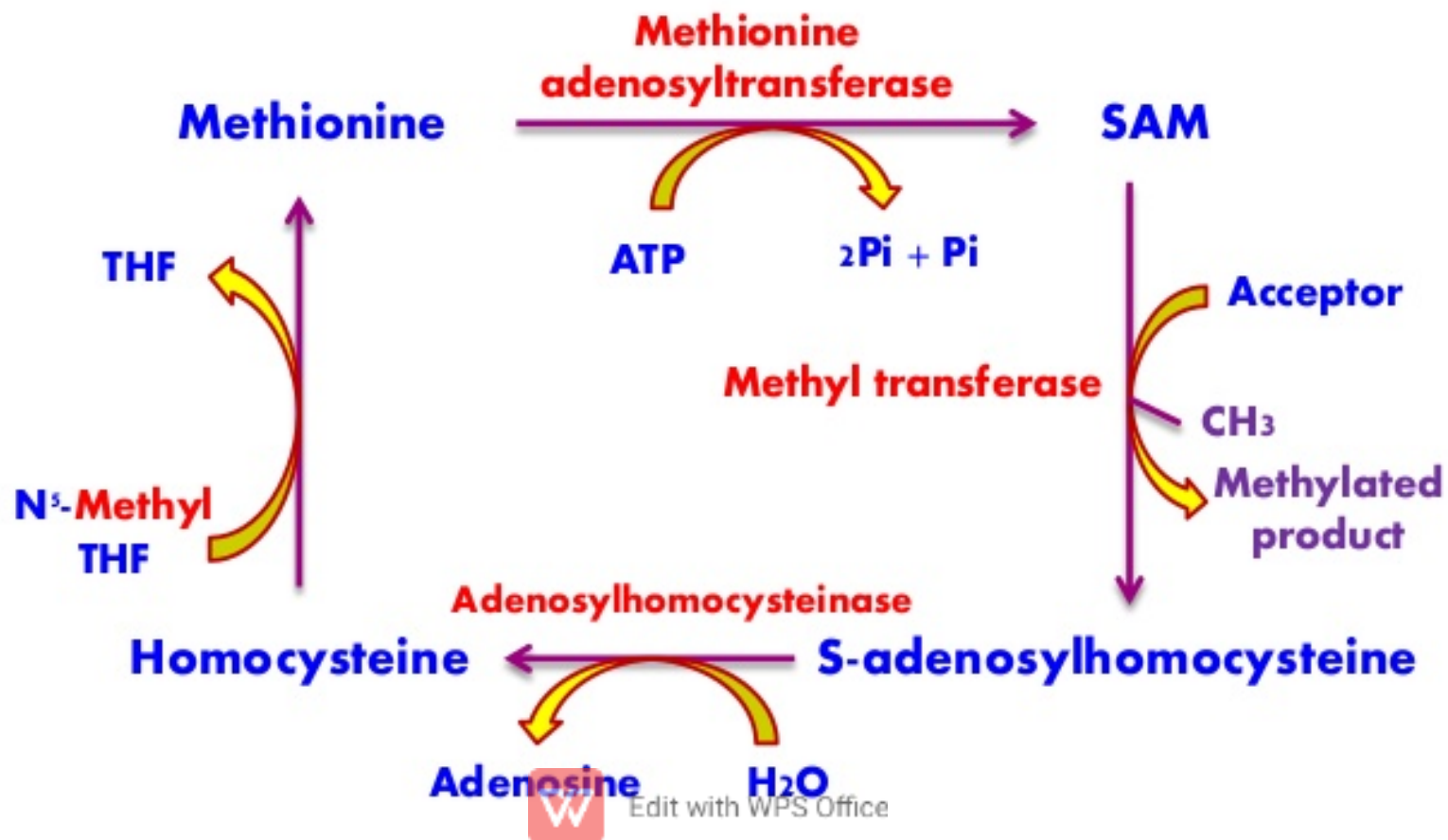
Methyl group acceptor	Methylated product
Guanidinoacetate	Creatine
Norepinephrine	Epinephrine
Epinephrine	Metanephrine
Ethanolamine	Choline
Nicotinamide	N-Methylnicotinamide
Acetyl serotonin	Melatonin
Phosphatidylethanolamine	Phosphatidylcholine
Serine	Choline
Carnosine	Anserine
t-RNA bases	Methylated t-RNA bases
Lysine	Methyl lysine



- **SAM is the donor in DNA methylation reactions which protects the DNA from digestion by its own restriction enzymes**
- **Methylation of DNA regulates gene expression**
- **Methylation of DNA helps in mismatch repair mechanism**



SAM-Cycle-synthesis, utilization & regeneration



- **Methionine synthesis:**
- **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.**
- **In this manner, methionine can be regenerated for reuse.**



Conversion of Methionine to Cysteine

1. Formation of S-adenosyl Methionine .
2. Formation of S-adenosyl Homocysteine.
3. Formation of Homocysteine.
4. Formation of Cysteine.



Homocysteine

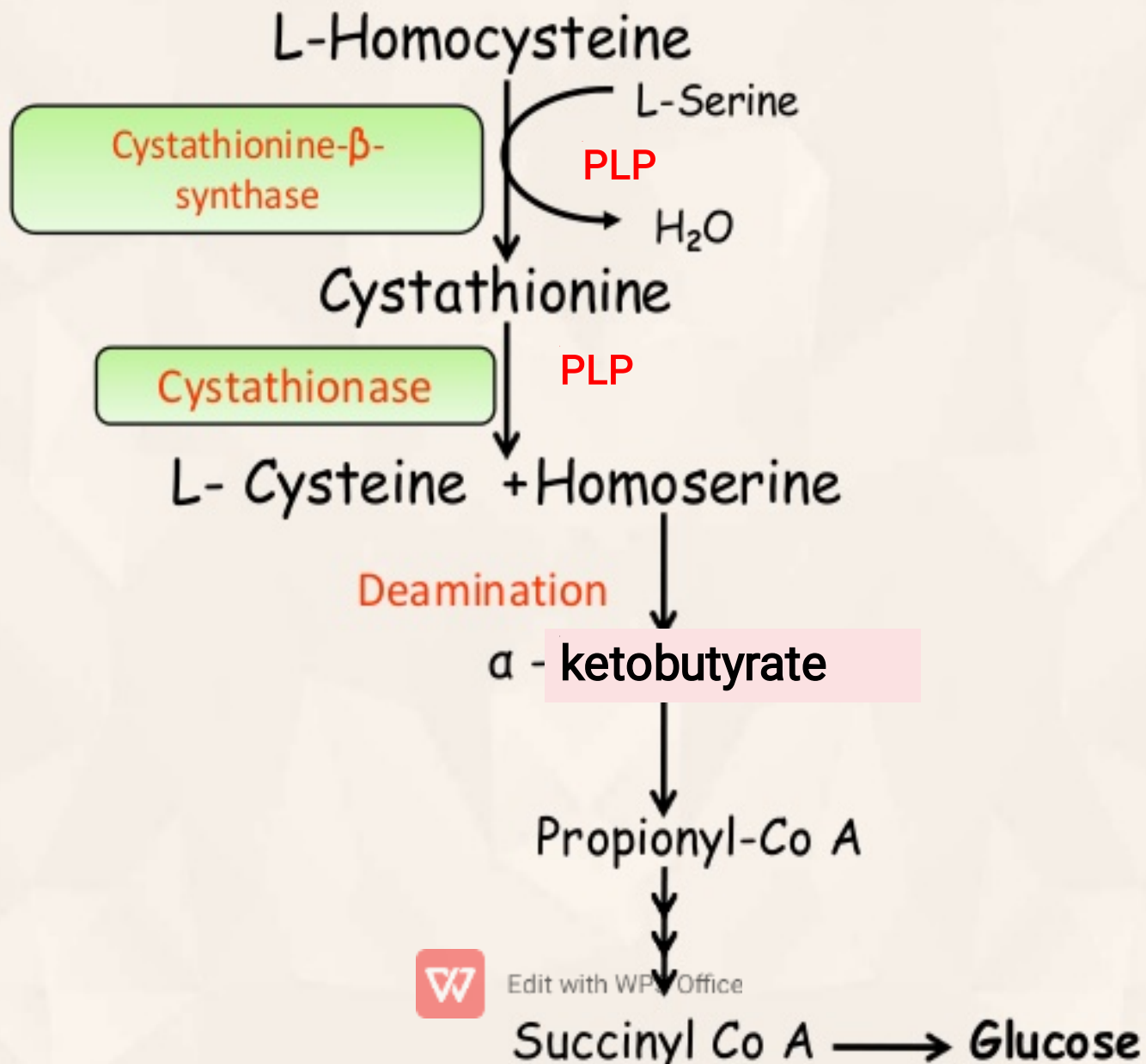
- On donating the methyl group SAM becomes S-adenosyl homocysteine. Enzyme is methyl transferase
- SAH releases adenosine group by enzyme adenosine homocysteinase : homocysteine is obtained

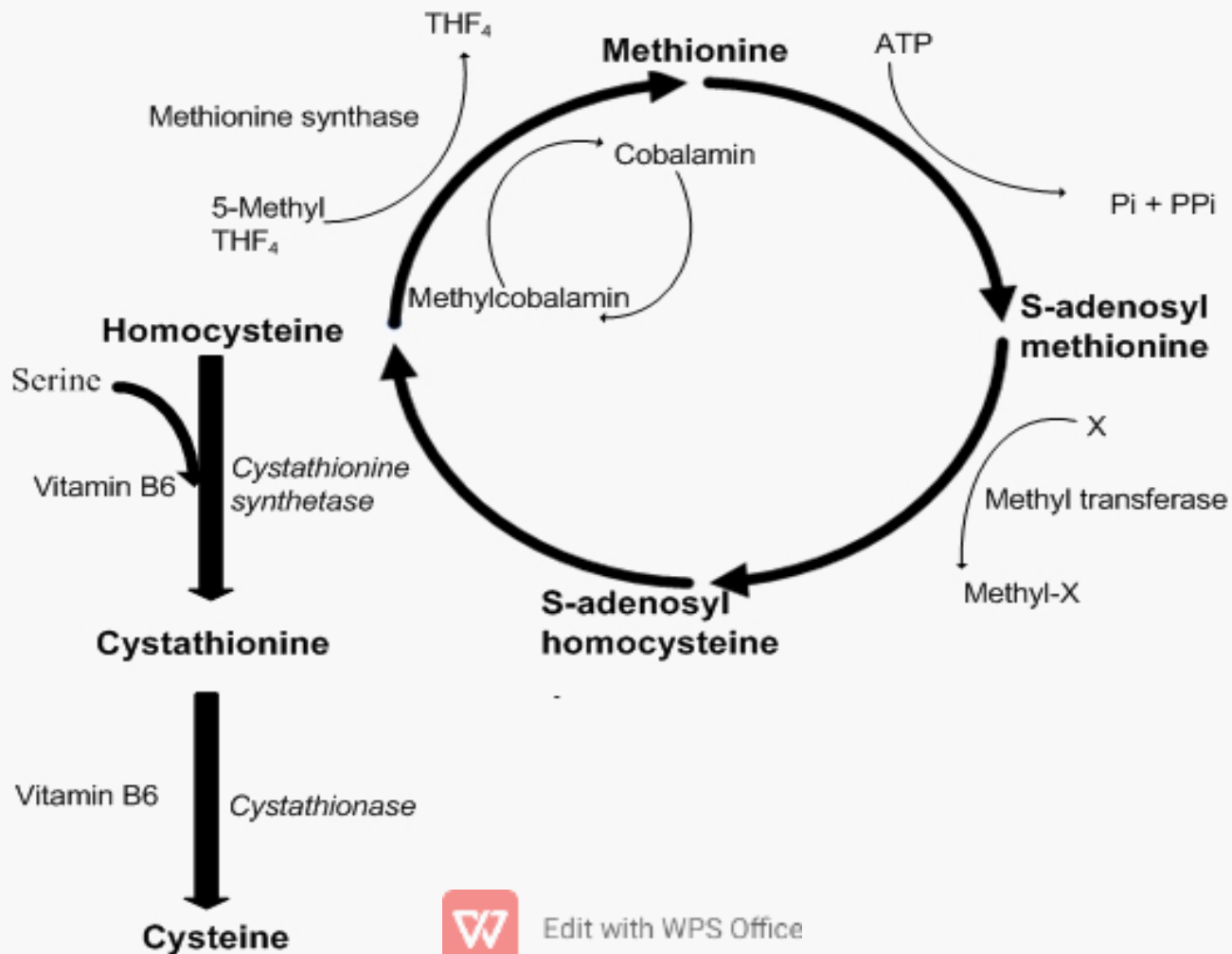


Fates of homocysteine

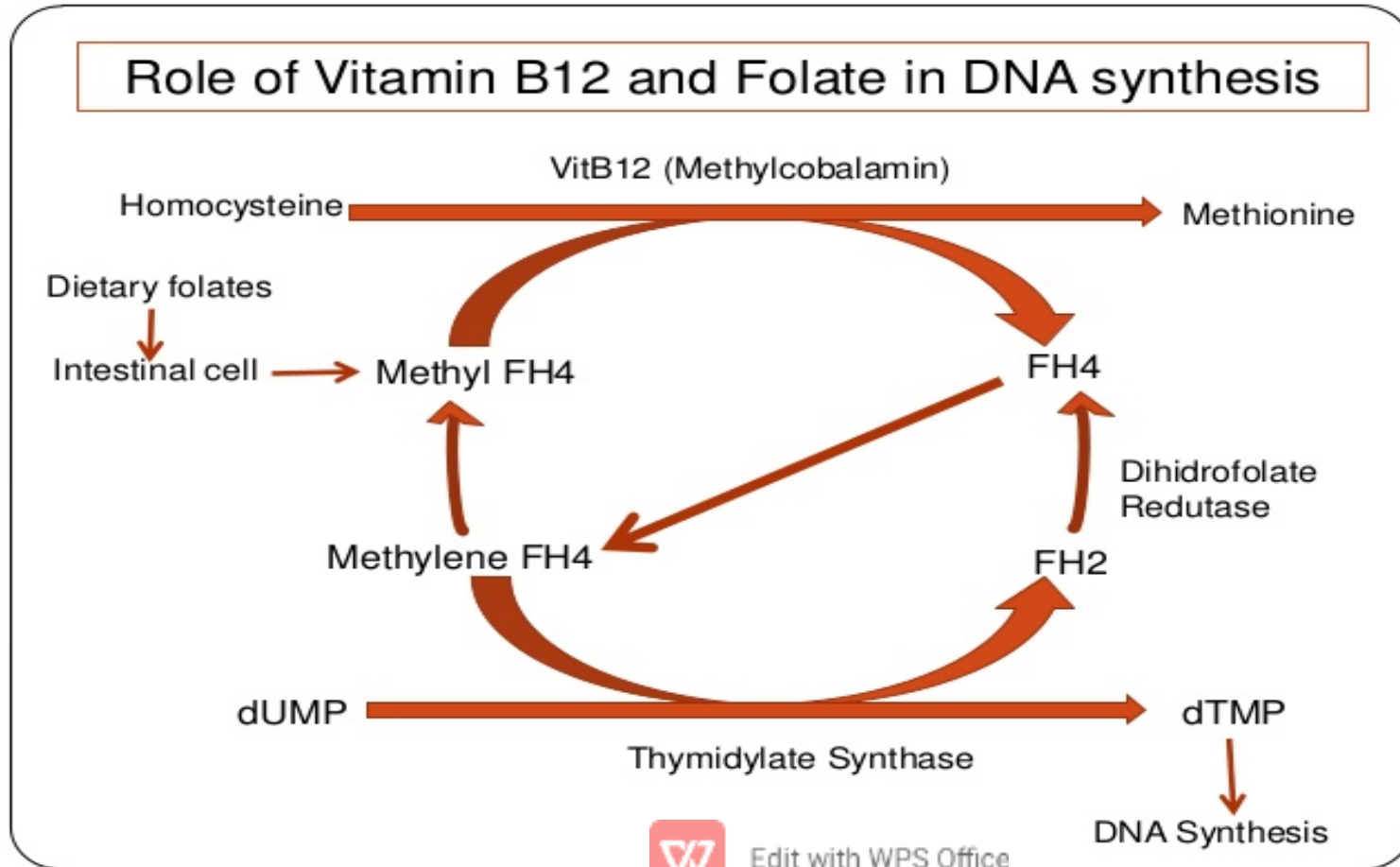
- Depending on the needs of body it can be converted to:
- 1. **succinyl CoA**: for gluconeogenesis
- 2. **cysteine**: trans sulphuration reaction
- 3. **methionine**: remethylation







Folate trap



Homocystinuria

- Disorder of methionine catabolism characterised by:
 1. urinary excretion of homocystine
 2. increased blood levels of homocysteine, homocystine and methionine



Types of Homocystinuria

Types	Defect
Homocystinuria-I	Cystathionine β synthase
Homocystinuria-II	N^5, N^{10} methylene THF reductase
Homocystinuria-III	N^5, N^{10} - Methyl THF homocysteine methyltransferase (leads to defect in synthesis of methylcobalamin)
Homocystinuria-IV	Defect intestinal absorption of vitamin B_{12}



- Four types are known:

type I: deficiency of cystathionine synthase

type II: deficiency of N5N10 MTHFR

type III: cobalamine Methyl transferase
deficiency

type IV: vitamin B12 deficiency

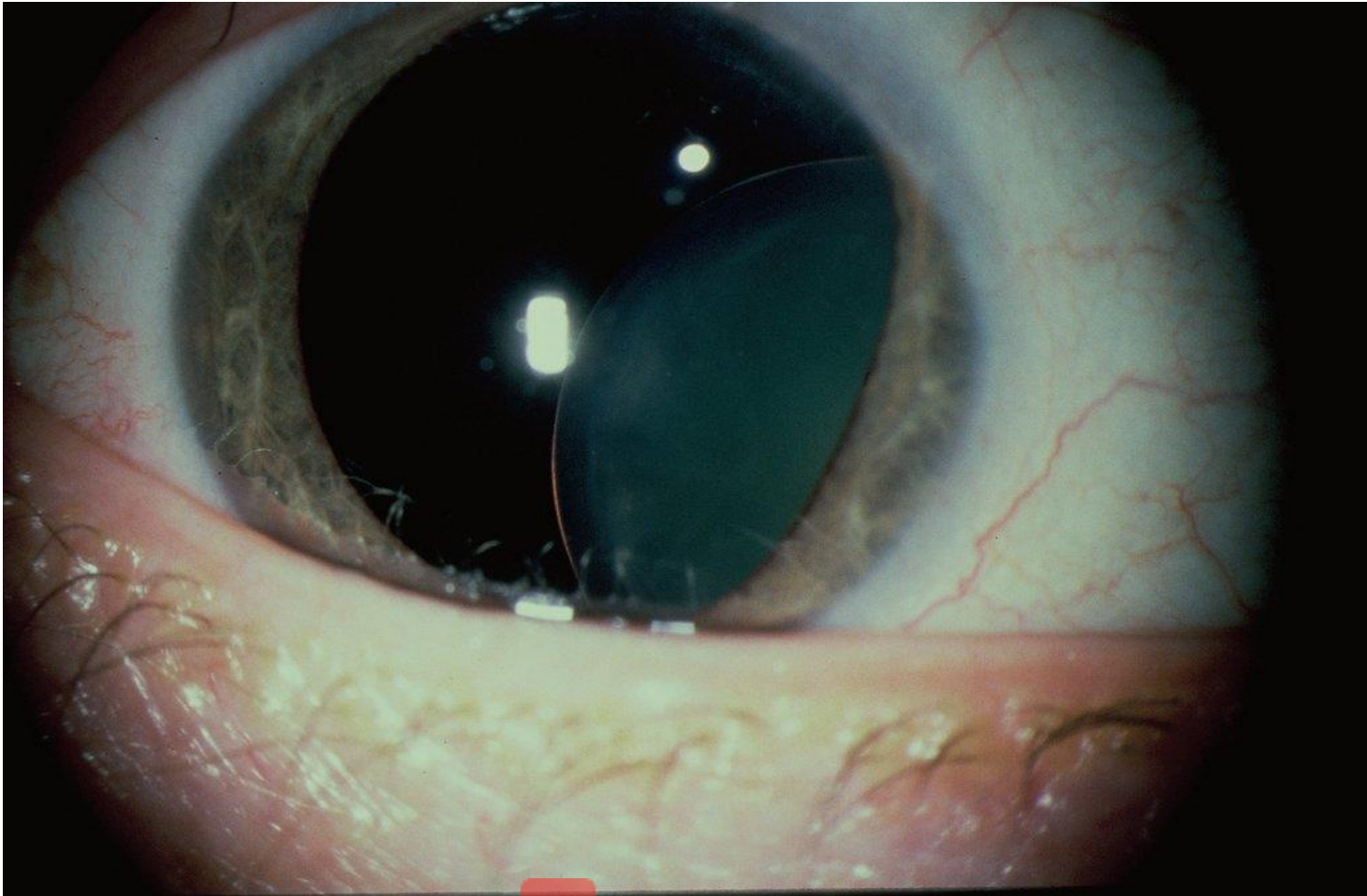
Clinical features

- Present by the age 3-5 years
- Ectopia lentis : subluxation of lens
- Mental retardation
- Osteoporosis



- **Charlie Chaplin gait**
- **Increased vascular thrombosis**





Edit with WPS Office



Figure 1: Wrist sign in Marfan syndrome (a), compared to normal (b).





Edit with WPS Office

Biochemical basis

- Homocysteine interacts with lysyl residues of collagen interfering with collagen cross linking
- Homocysteine binds to fibrillin and leads to defects in elastin and fibrillin: subluxation of lens , marfanoid habitus



- **Homocysteine thiolactone is a reactive free radical: thiolates LDL leading to LDL oxidation and endocytosis by macrophages**
- **Interference with collagen cross linking leads to endothelial dysfunction and thrombosis**



DIAGNOSIS

- Screening: cyanide nitroprusside test: positive in urine
- Cyanide reduces homocystine to homocysteine . SH group gives red colour with nitroprusside
- Cysteine can give false positive results
- Differentiated by silver nitroprusside test: positive only for cysteine



- **Confirmatory diagnosis:** estimation of cystathionine synthase and homocysteine levels in plasma(normal 5-15 mmol/l)
- **TREATMENT:** dietary restriction of methionine

B6, folate and B12 supplementation



Cystathionuria

- Deficiency of cystathionase
- MR, anemia, thrombocytopenia



CYSTEINE

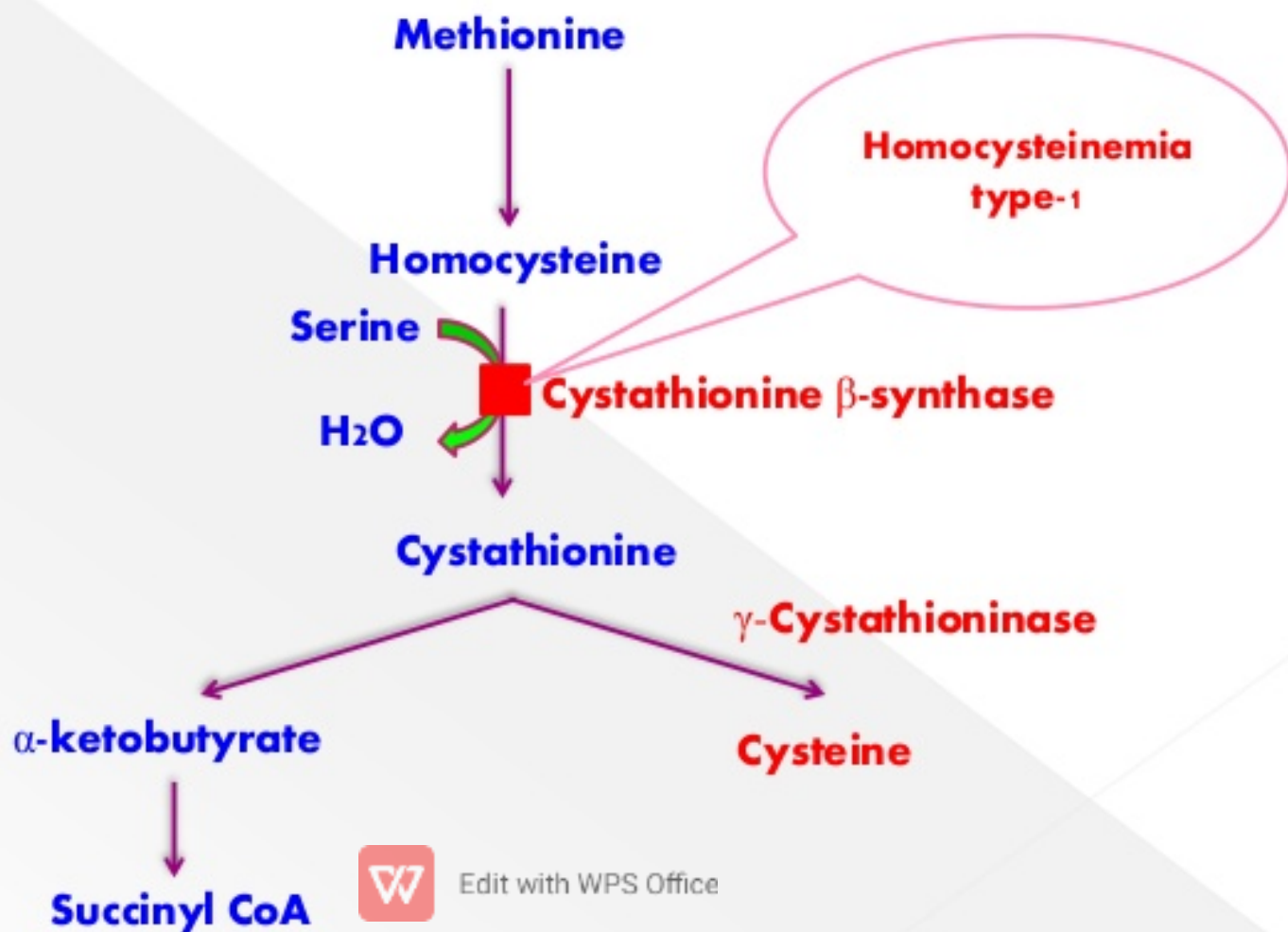


Edit with WPS Office

- **From methionine: by trans-sulphuration**
- **From cystine: by cystine reductase**
2 molecules of cysteine are produced



Synthesis of cysteine from methionine

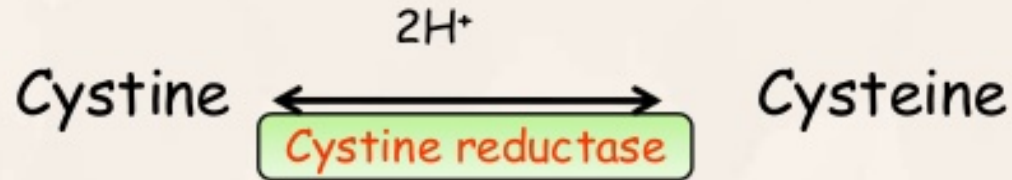


Fates of cysteine ☒ and important products



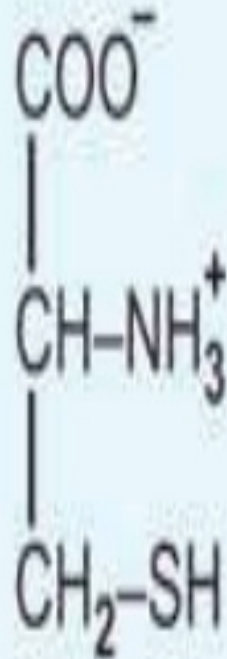
Degradation of cysteine

- ⊙ **Cystine & cysteine are interconvertible by an NAD^+ dependent cystine reductase.**



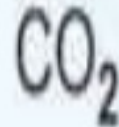
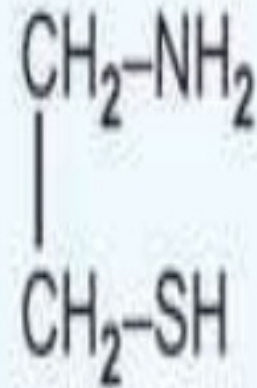
Decarboxylation Cysteine

Cysteine

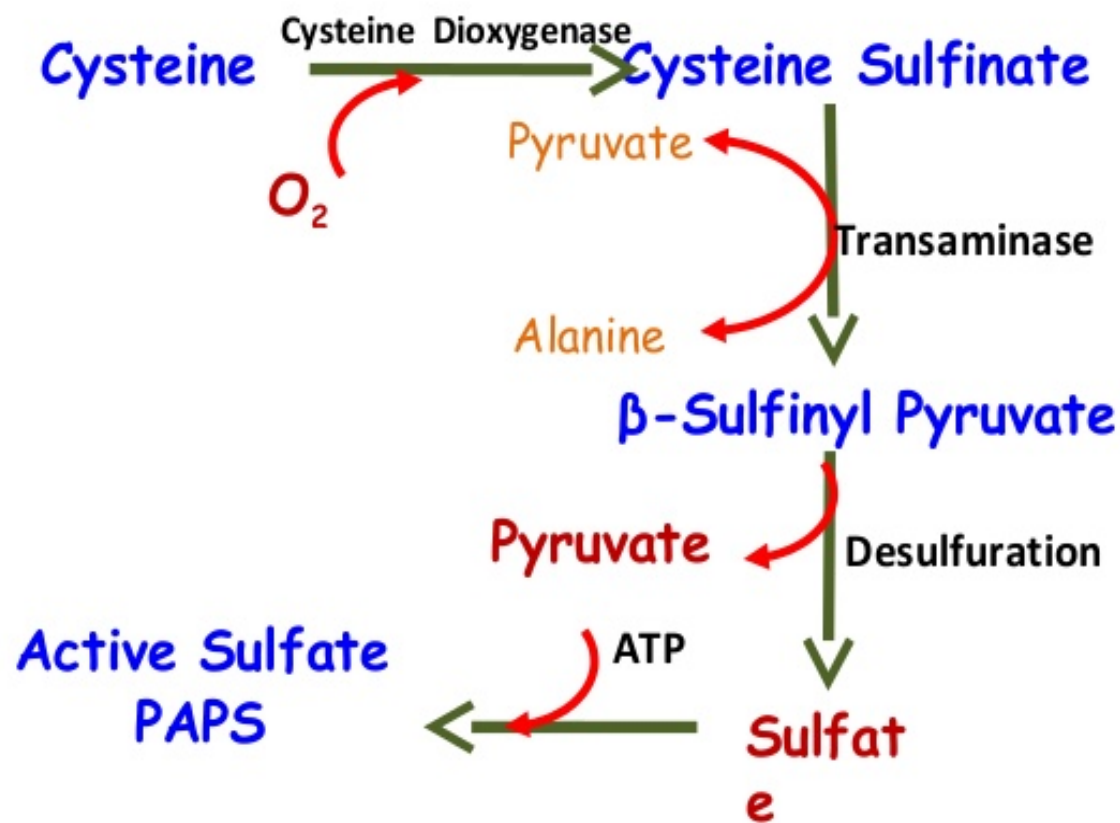


Decarboxylase, PLP

Beta-mercapto
ethanolamine

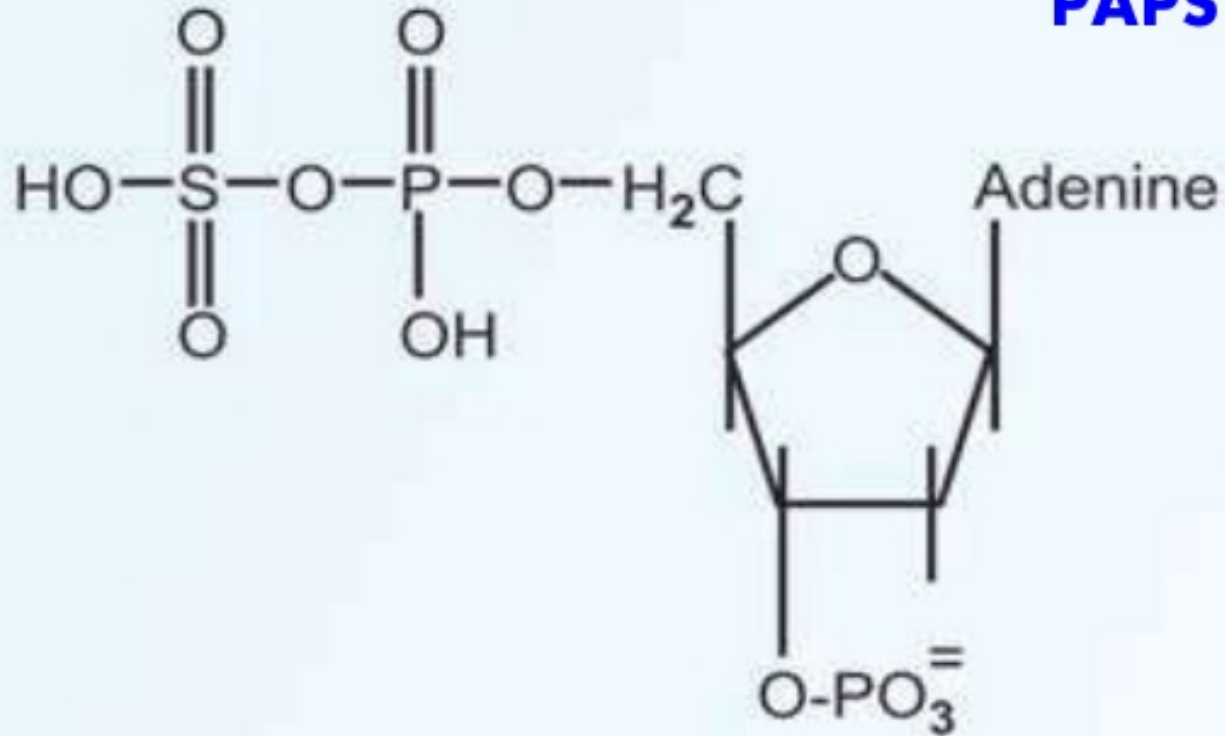


Cysteine to Active Sulfate





PAPS



3'-phosphoadenosine 5'-phosphosulfate (PAPS)

- ① **Cysteine sulfinic acid cleaves off alanine to produce sulfite which is converted to sulfate & excreted in urine.**
- ② **Some amount of sulfate condenses with ATP to form active sulfate or 3'-phosphoadenosine 5'-phosphosulfate (PAPS).**



- ① **Active sulfate (PAPS) is utilized for the synthesis of mucopolysaccharides.**
- ① **Used in detoxification.**
- ① **Sulfate is also a structural component of proteins & lipids.**



GLUTATHIONE

- ⦿ **Cysteine is required for formation of Glutathione.**
- ⦿ **Glutathionine is required for transport of amino acids.**
- ⦿ **Glutathione is present in the RBCs.**
- ⦿ **This is used for inactivation of free radicals formed inside RBC.**

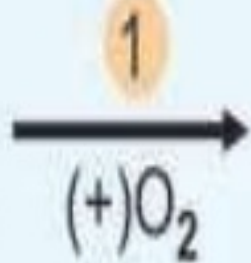
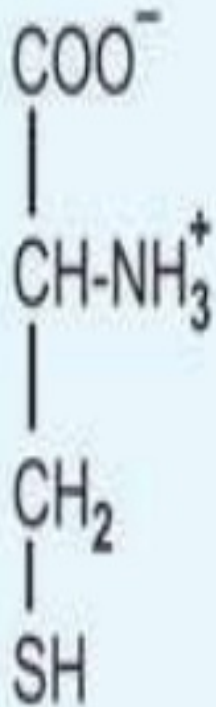


- ① **Glutathione helps to detoxify several compounds.**
- ② **Glutathione keeps the enzymes in reduced, active state.**
- ③ **Cysteine residues in polypeptide chains form disulfide bridges to make active proteins, e.g. insulin & immunoglobulins.**

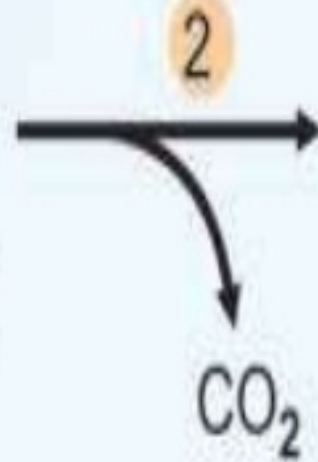
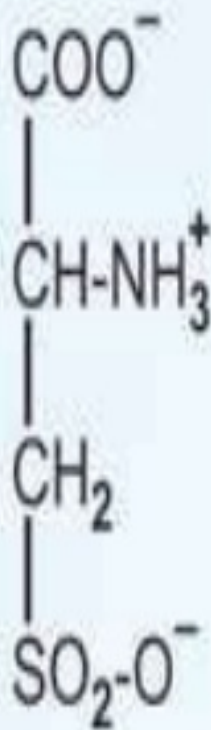


Formation of taurine from cysteine

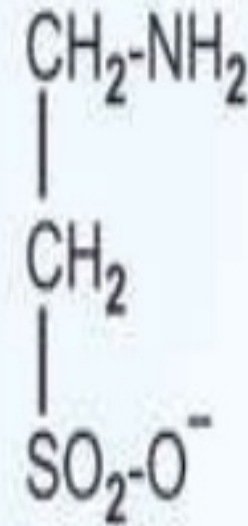
Cysteine



Cysteic acid



Taurine



1. Cysteine dioxygenase, 2. Decarboxylase

Functions of TAURINE

- Bile acid conjugation
- Inhibitory neurotransmitter
- Modulator of calcium fluxes, helps in calcium binding and movement
- Antioxidant role
- Essential in development of CVS and skeletal system
- osmoregulation



Fates of sulphur

- Sulphur is excreted in urine as:
- Inorganic sulphates
- Etheral sulphates
- Neutral sulphur



Inborn errors of sulfur amino acid metabolism

- ⊙ **Cystinuria (cystine-lysinuria):**
- ⊙ **The most common inherited disease.**
- ⊙ **It is characterized by increased excretion of cystine (25-40 times normal).**
- ⊙ **Elevation in the urinary output of lysine, arginine & ornithine is also observed.**



- **Cystine-lysinuria (Garrod's tetrad) : Transport defect of cystine**
- **Cystine, Ornithine, Lysine, Arginine are excreted in urine**
- **Patients present with renal stones**
- **Urine cyanide nitroprusside test is positive**



Cystinosis (cystine storage disease)

- ⊙ **Cystine crystals are deposited in many tissues & organs of reticuloendothelial system throughout the body.**
- ⊙ **These include spleen, lymph nodes, liver, kidney, bone marrow etc.**
- ⊙ **A defect in the lysosomal function.**
- ⊙ **Cystine accumulates in the lysosomes of various tissues.**



Cystinosis

- Cysteine transporter defect in lysosomal membrane
- Cystine accumulates in lysosomes of liver, spleen, bone marrow, cornea.
- Microscopy shows cystine crystals in WBC
- Renal failure in about 10 years
- Treatment: alkalinization of urine and drugs like penicillamine



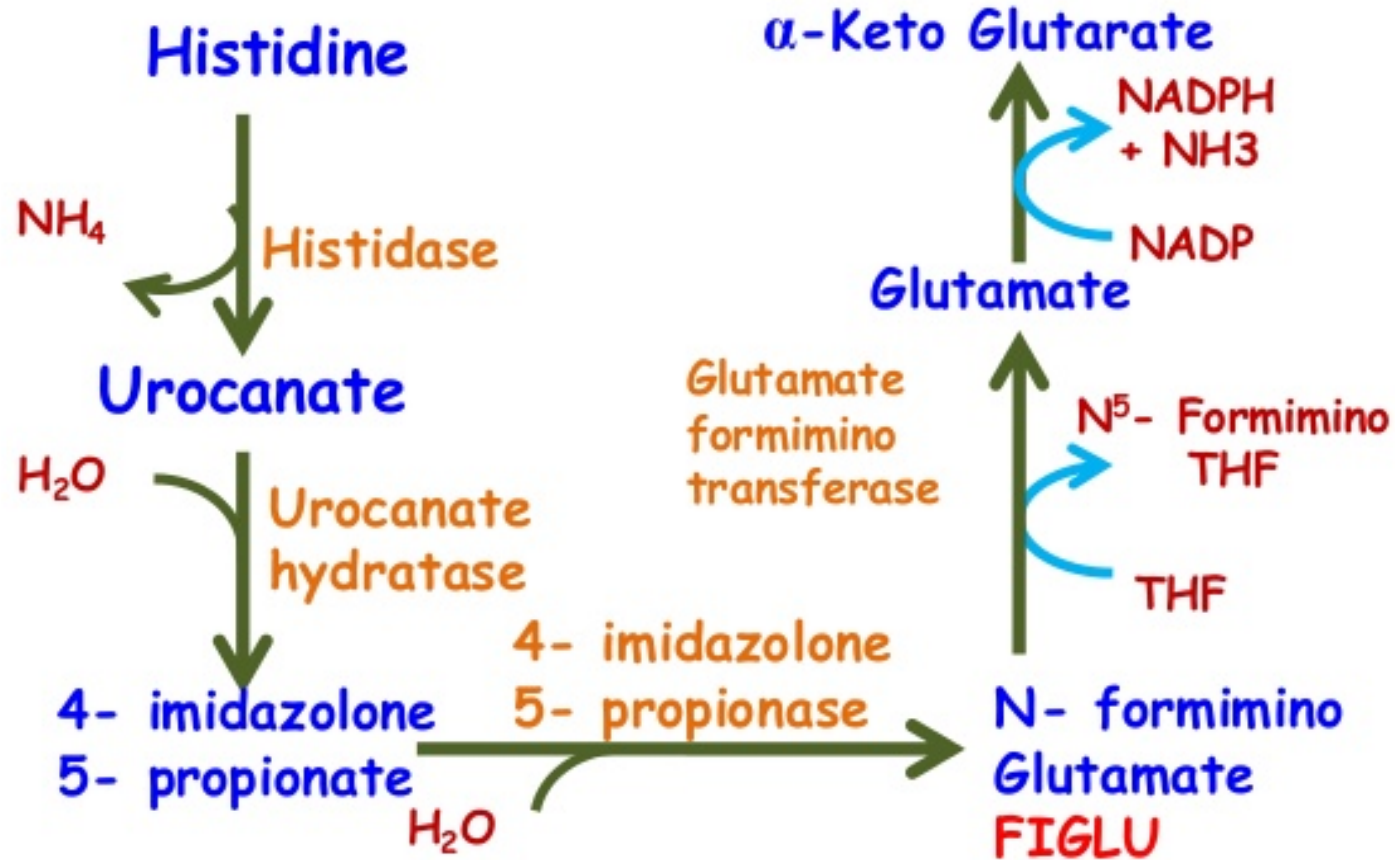
HISTIDINE

- Imidazole ring containing amino acid
- Semi essential
- Responsible for buffering action of proteins
- Precursor of histamine, carnosine and anserine
- Glucogenic amino acid



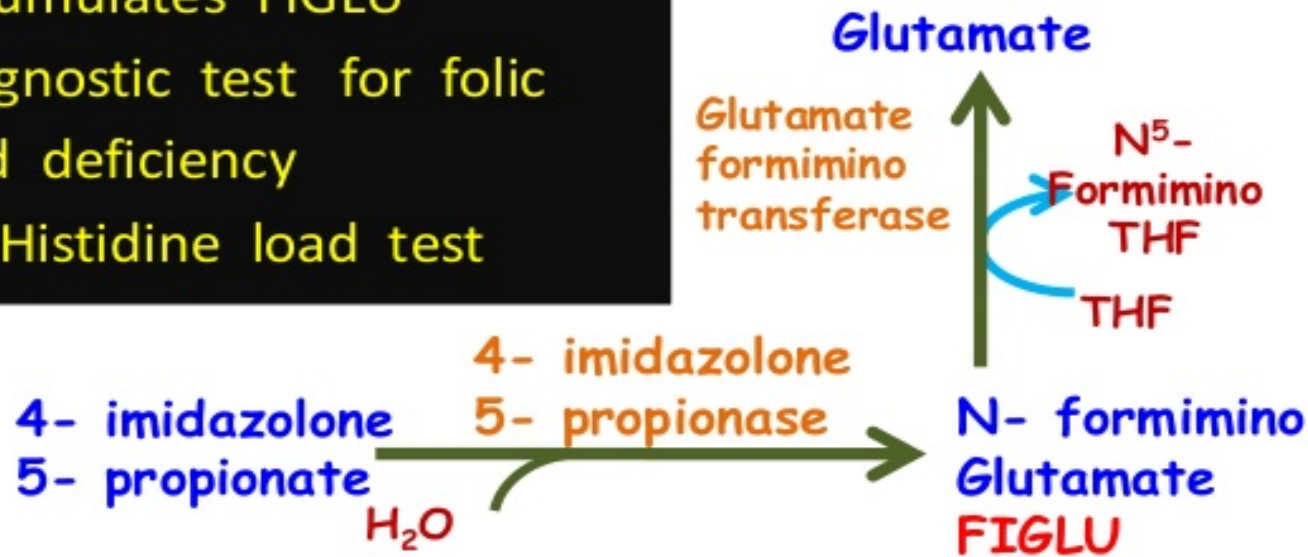
His

Metabolism of Histidine

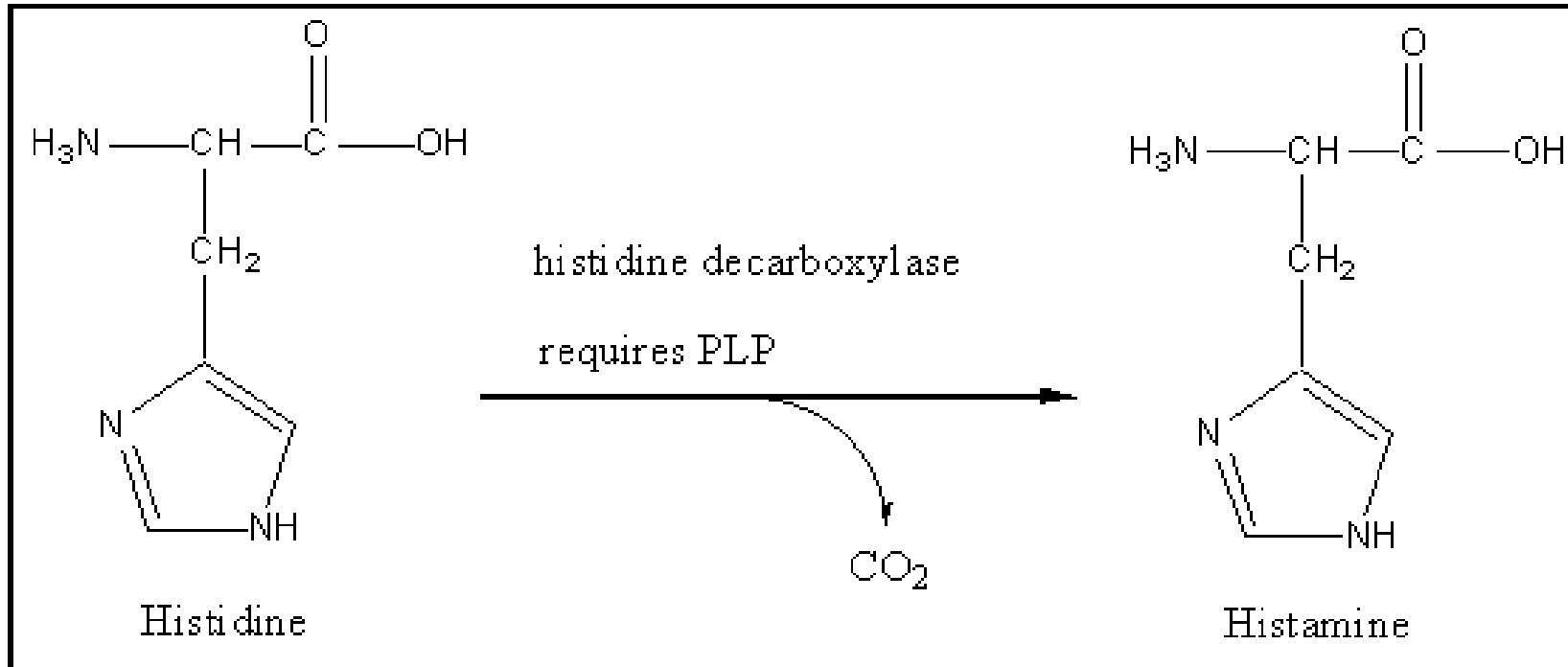


Metabolism of Histidine

Deficiency of folic acid
accumulates FIGLU
Diagnostic test for folic
acid deficiency
by Histidine load test



HISTAMINE SYNTHESIS



- **Histamine is synthesised in platelets, basophils, mast cells, brain, stomach.**
- **It is responsible for anaphylactic reactions**



Role of histamine

Tissue	role
Blood vessels	vasodilation
CVS	Fall in BP, increased capillary permeability
Heart	Chronotropic and inotropic effect, increases coronary artery flow
Smooth muscles	contraction
Exocrine glands	Stimulates gastric secretion



FIGLU TEST

- This is a test done to assess the deficiency of folic acid
- 5 gm of histidine is given three times at intervals of 4 hours
- Urine is collected for 24 hours after initial dose
- Normally less than 30 mg of FIGLU is excreted per day
- Increased FIGLU excretion occurs in folic acid deficiency



Serine

- Phosphatidyl serine
- Sphingomyelin and cephalin synthesis
- Involved in enzyme activities



ONE CARBON METABOLISM



Edit with WPS Office

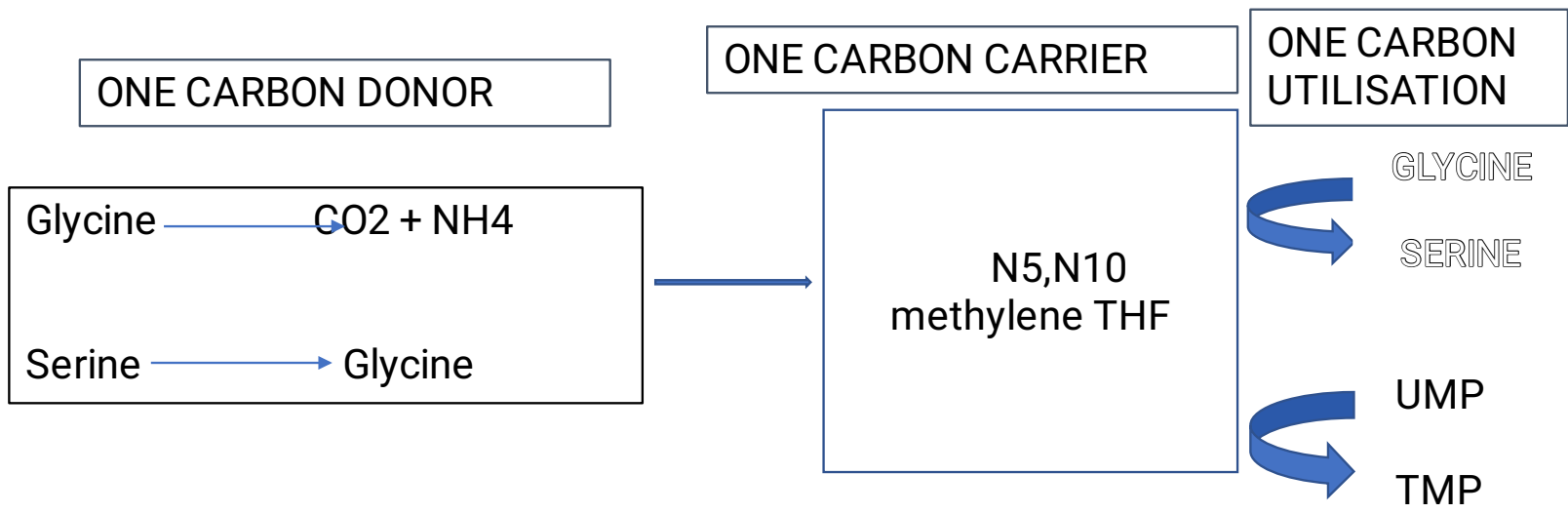
- **One carbon group plays an important role in synthesis of different compounds in the body**
- **Most of the one carbon transfers are promoted by one of the three cofactors—THF, S-adenosine methionine and biotin.**
- **The one carbon group is covalently attached to THF at N5 or N10 positions or both**

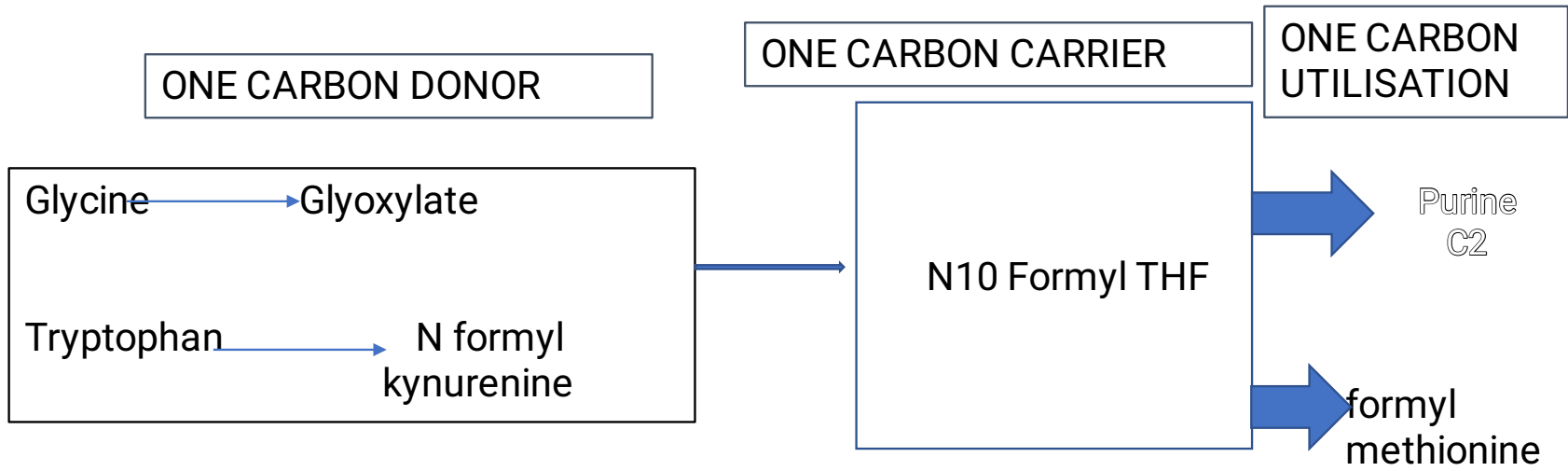


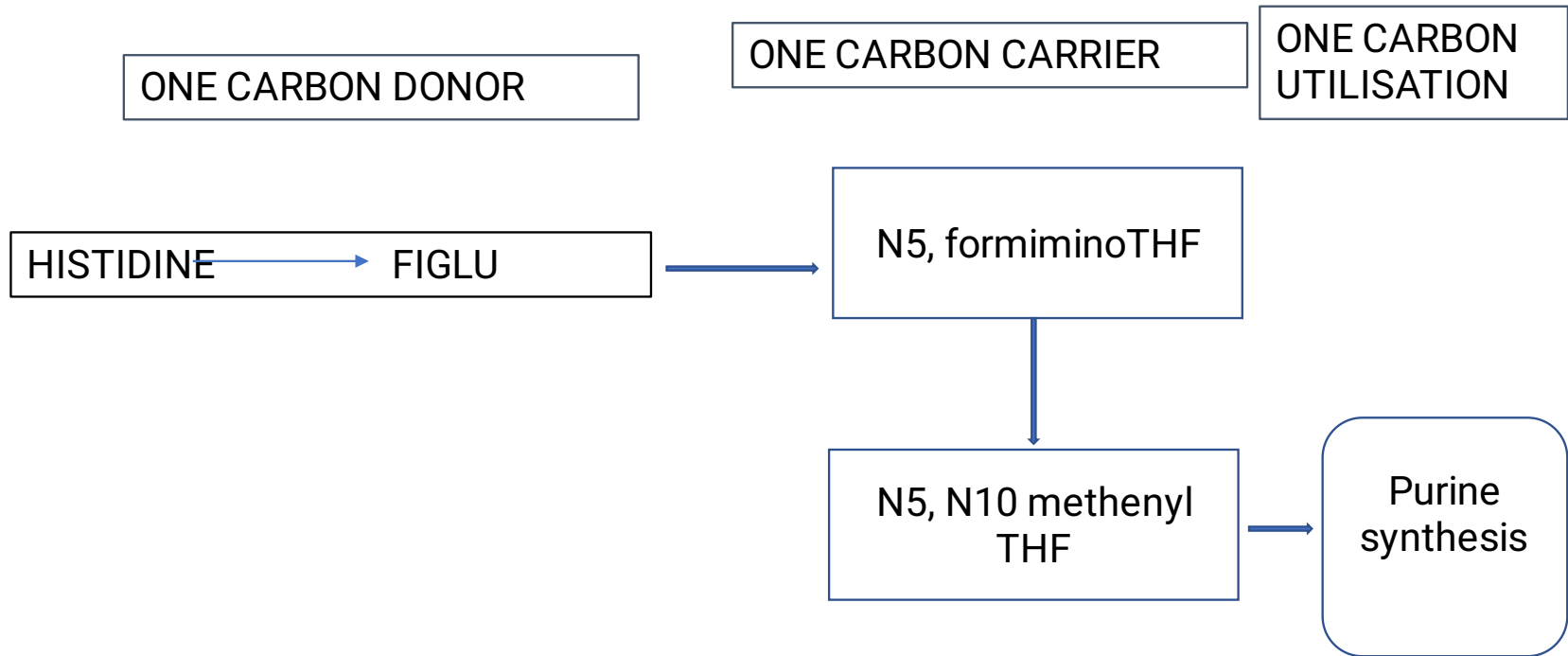
One carbon groups

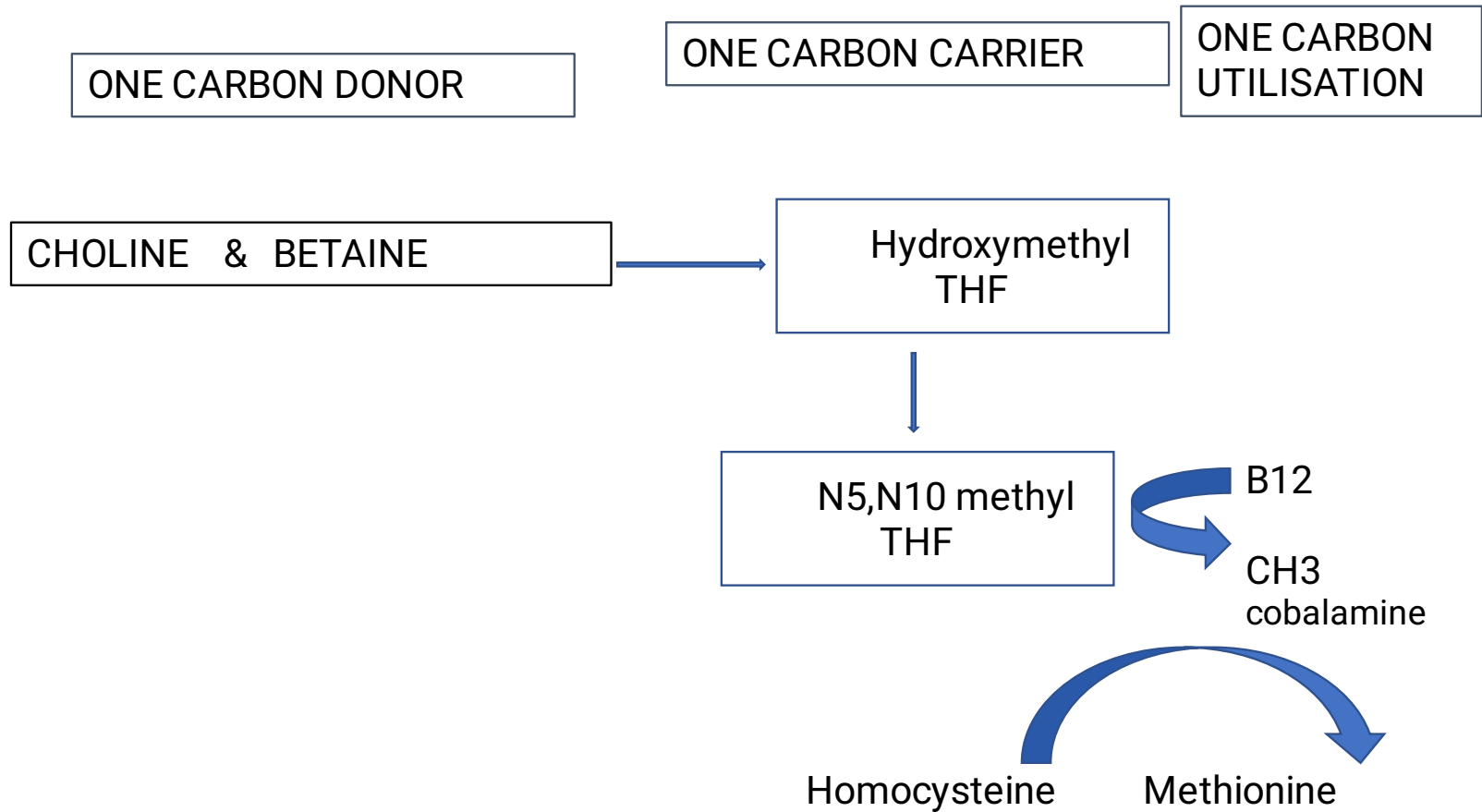
<u>Oxidation State</u>	<u>Structure</u>	<u>Name</u>
Most reduced	-CH ₃	Methyl
Intermediate	-CH ₂ -	Methylene
Most oxidized	-CHO -CHNH -CH=	Formyl Formimino Methenyl











Glutamic acid

- Plays a central role in metabolism of aminoacids
- **IMPORTANT PRODUCTS:**
 1. NAG is a positive regulator of urea cycle
 2. Glutamine
 3. GABA
 4. Glutathione
 5. Excitatory neurotransmitter : acts through NMDA receptors



GABA

- Synthesised by decarboxylation of glutamic acid
- Inhibitory neurotransmitter
- Opens up chloride channels in post synaptic membranes in CNS
- Both formation and degradation requires PLP
- Low levels can lead to convulsions. Antiepileptic drugs like valproate inhibits GABA breakdown

Glutamine

- N 3 and 9 in purine, N 3 in pyrimidine
- Donor of amino group in synthesis of NAD
- Conjugating agent
- Acidification of urine



ASPARTIC ACID ☒

- Used for synthesis of purine and pyrimidine
- Used in urea cycle



Asparagine

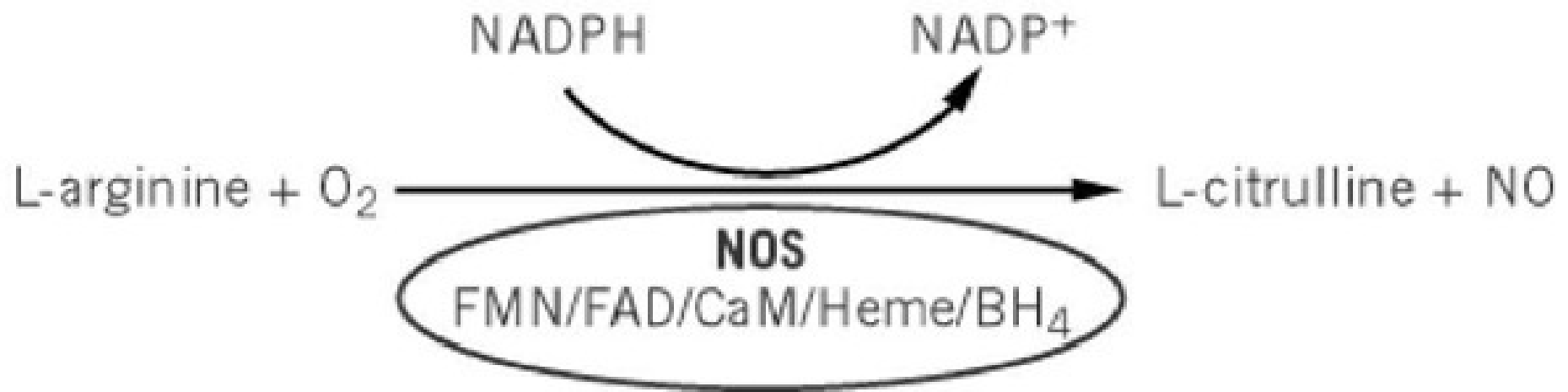
- Glucogenic amino acid
- Present in almost all the proteins
- L- asparaginase is anti cancer drug used in leukemia and lymphomas
- The cancer cells cannot synthesize asparagine so the cells die.



ARGININE

- Source of :
 1. urea,
 2. creatine,
 3. nitric oxide





Nitric oxide (NO)

- ⊙ Arginine is the substrate for the production of nitric oxide (NO).
- ⊙ The **enzyme nitric oxide synthase** (three isoenzymes) cleaves the nitrogen from the guanidino group of arginine to form NO.
- ⊙ **Requires** NADPH, FMN, FAD, heme & tetrahydrobiopterin.
- ⊙ **Very short half-life** (about 5 seconds)



Nitric Oxide Synthase isoenzymes

- **NOS I**
 - Central and peripheral neuronal cells
- **NOS II**
 - Most nucleated cells, particularly macrophages
- **NOS III**
 - Vascular endothelial cells



Biochemical role of NO

- Also known as EDRF, it is a vasodilatory molecule
- Vasodilation of coronary, cerebral, renal and muscle arteries
- neurotransmitter in CNS: stimulates the release of CRH, GHRH, LHRH
- Macrophage: NO forms peroxynitrite which is lethal to microorganisms
- Platelets: NO inhibits platelet adhesion

- Intestine: NO is a NANC neurotransmitter in GIT and urogenital tract.
- It relaxes smooth muscles and leads to decreased gastrointestinal motility and relaxation of the sphincters.

NO as therapeutic agent

- Nitrates are used for treatment of angina pectoris
- Used in pulmonary hypertension
- Treatment of erectile impotence



Mechanism of action

- **Increases c GMP by activating guanylate cyclase in smooth muscles**
- **This increases the levels of c GMP**
- **This activates myosin kinase in smooth muscles leading to relaxation.**
- **Thus NO acts as vasodilator**



Fates of NO

- NO combines with oxygen to form NO₂
- This is excreted through urine

- It combines with superoxide ion to form nitric oxide free radical and also peroxynitrite (OONO⁻) which are harmful free radicals



POLYAMINES

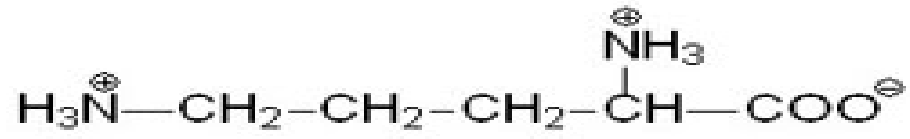
- Putrescine, spermidine and spermine are called polyamines.
- They are synthesised from ornithine with the help of methionine.
- DFMO is a powerful inhibitor of polyamine synthesis and is used in treatment of African sleeping sickness.
- It is an example of suicide inhibition.



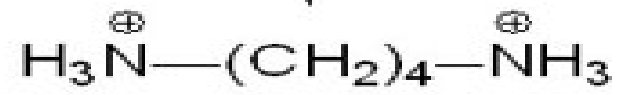
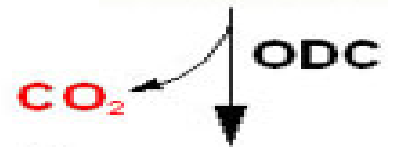
Biosynthesis

- ⊙ **Ornithine & S-adenosylmethionine are the precursors for polyamine synthesis.**
- ⊙ **The four carbon moiety of SAM (not the methyl group) involved in polyamine formation.**
- ⊙ **Ornithine decarboxylase acts on ornithine to split off CO₂ & produce putrescine.**

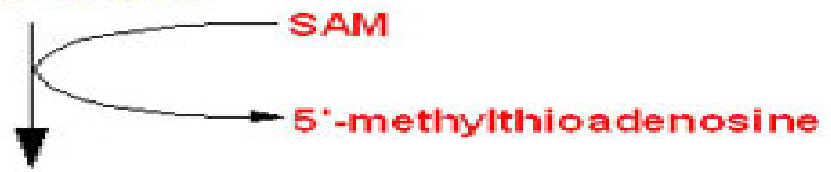




Ornithine



Putrescine

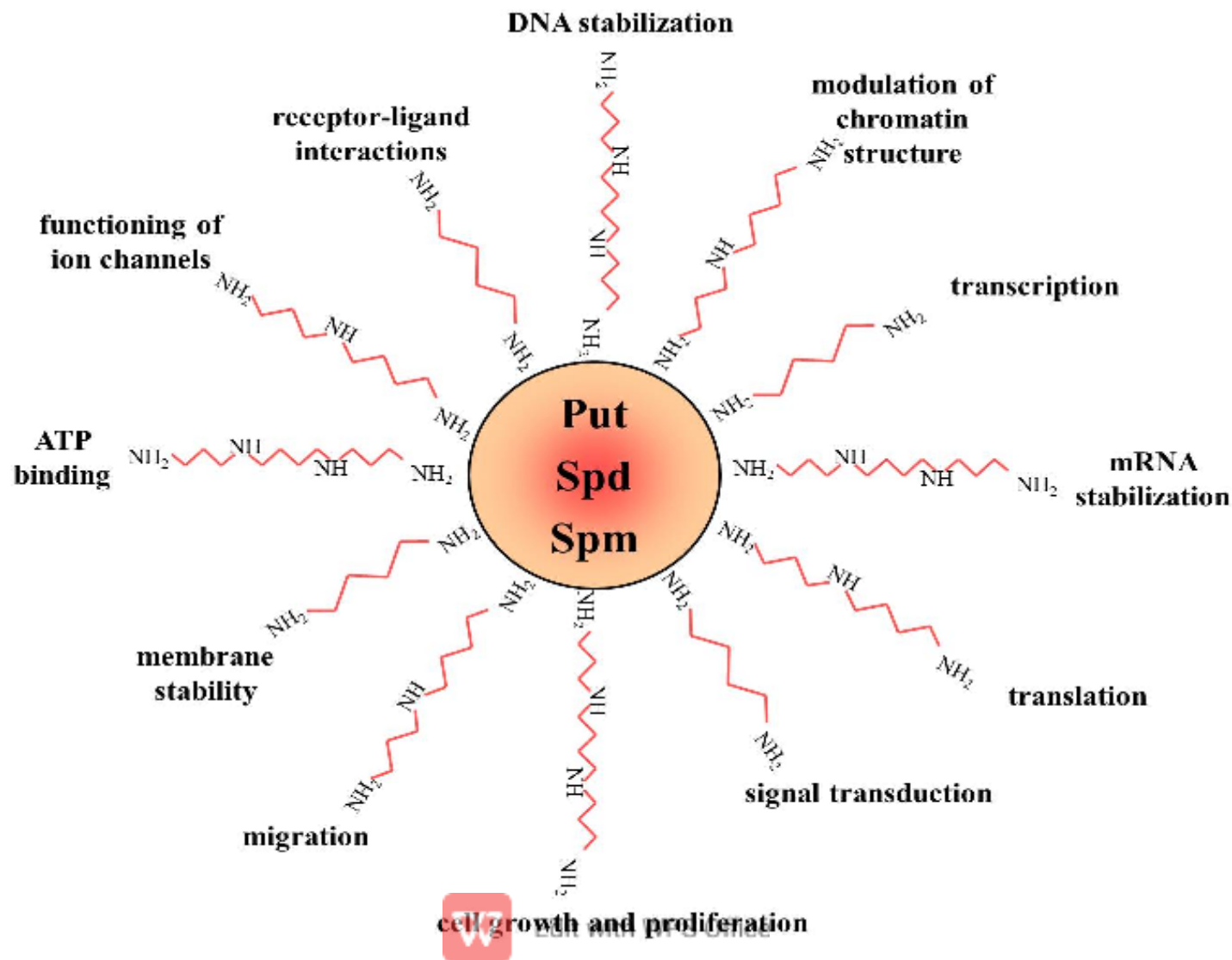


Spermidine



Spermine





BIOGENIC AMINES

- Biogenic amines are the products formed from decarboxylation of amino acids
- PLP is required for the reaction
- They have significant functions in our body
- A list of biogenic amines is as follows



Substrate	Decarboxylated products	Functions/significance
Serine	ethanolamine	Required for choline synthesis
tyrosine	tyramine	Present in chocolates, cheese, buttermilk etc: precipitates migraine
DOPA	dopamine	Catecholamine, neurotransmitter in EPS
tryptophan	tryptamine	Formed in intestine by putrefaction
5-OH tryptophan	serotonin	neurotransmitter

Substrate	Decarboxylated product	Functions/significance
cysteine	taurine	Bile salt conjugation, neurotransmitter, modulator of calcium fluxes
histidine	histamine	Mediator of allergic reactions, vasodilator
ornithine	putresine	Polyamine: cell division and protein biosynthesis
Glutamic acid	GABA	Inhibitory neurotransmitter in CNS.



AMINOACIDURIA

- **Definition:** A metabolic disorder where excess of aminoacids are present in urine
- The term aminoaciduria is applied when more than 5% of the filtered load is detected in the urine.
- **Classification:**
 - Primary : due to enzyme defect in metabolism of aminoacids e.g: phenylketonuria
 - Secondary : due to defect in aminoacid transporter in kidney or intestine e.g: cytinuria, hartnup's disease



Fanconi's syndrome


- It is the most common inherited aminoaciduria.
- The syndrome is characterised by a generalised aminoaciduria and by other renal tubular defects affecting reabsorption of phosphate and glucose.
- renal handling of potassium and water are also affected.



Disorder	defect	Clinical features
phenylketonuria	Phenylalanine hydroxylase	MR, mousy odour of urine, hypopigmentation
homocystinuria	Cystathionine synthase	Dislocation of lens, gait abnormalities, premature atherosclerosis
alkaptonuria	Homogentisate oxidase	Darkening of urine on standing, alkapton bodies in soft tissues and joints
Maple syrup urine disease	Branch chain ketoacid decarboxylase	MR, seizures, urine smells like burnt sugar

Secondary aminoacidurias

Disorder	defect	Clinical features
cystinuria	Cysteine transporter	Cysteine, lysine, arginine and ornithine in urine, kidney stones
Hartnup's disease	Neutral aminoacid transporter in kidney, intestine	Pellagra like features

 Edit with WPS Office