Department of Biochemistry

Learning Objectives

- Fates of Amino Acids
- Sources of Amino Acids
- Amino Acid Utilization
- Nitrogen Balance
- Amino-group metabolism
- Transamination
- Deamination
- Transdeamination
- Transamidation
- Decarboxylation
- Transmethylation

Role of Glutathione in Amino Acid Absorption

- Meister proposed that glutathione participates in an active group translocation of L-amino acids (except L-Pro) into cells of small intestine, kidneys, seminal vesicles, and brain.

- He proposed a “cyclic” pathway/γ-glutamyl cycle in which Glutathione is regenerated again

- γ-glutamyl transferases (GGT) plays a key role in this cycle, a pathway for synthesis and degradation of glutathione and drug and xenobiotic detoxification

γ-glutamyl/Meister cycle

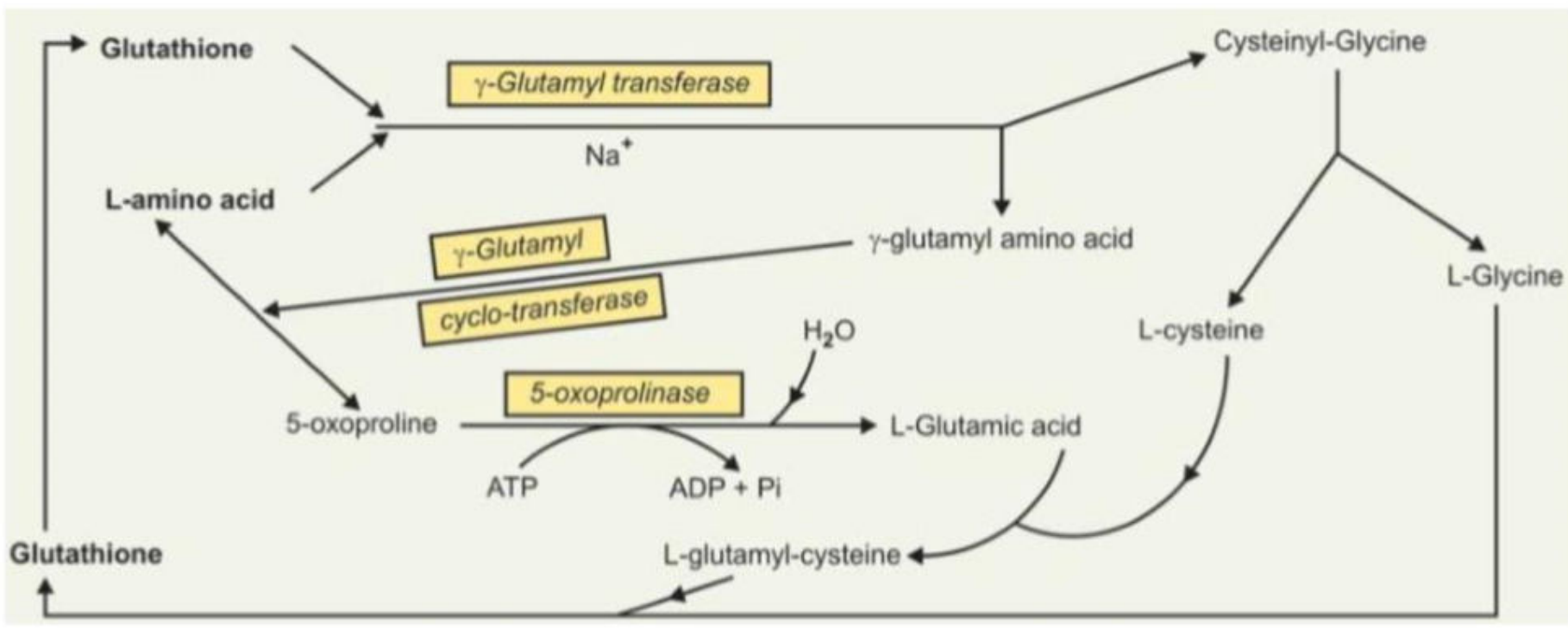

Fig.26.1: Text Book of Medical Biochemistry by Chatterjee & Rana Shinde, 8th Ed

Disorder related to aa transporter

Hartnup disease: Defect in SCL6A19 gene, it is a sodium-dependent and chloride independent neutral aa transporter, expressed in kidneys and intestine

- This gene controls the absorption of certain aa from intestine and reabsorption of those aa in kidneys
- Person with Hartnup disease cannot absorb aa properly from intestine and cannot reabsorb them from tubules in kidneys

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- Resulting excessive amount of aa such as Trp excreted in urine
- Due to inadequate amount of Trp, body not able to make sufficient amount of niacin (vit B3), which is necessary component of NAD^+
- Pellagra, a similar condition, is also caused by low nicotinamide; this disorder results in dermatitis, diarrhea, and dementia

Cont--

- Cystinuria: Dibasic (diamino aa) transporter Lys, Arg, Ornithine and Cys. If there is any defect in this transport system, it leads to Cystinuria

- In medicine, Garrod's tetrad is a term named for British physician Archibald Garrod, who introduced the phrase “inborn errors of metabolism" in a lecture in 1908

- Tetrad comprises four inherited metabolic diseases: albinism, alkaptonuria, Cystinuria and pentosuria

Fates of Amino Acids

- For Protein synthesis
- For synthesis of other nitrogen containing compounds (heme, creatine, purines, pyrimidines, choline, neurotransmitters)
- For the gluconeogenesis
- Energy source from glucogenic aa and ketogenic aa

Glucogenic aa: 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. Ex. Ala & Arg

Cont--

Ketogenic aa: Lysine and leucine are the only aa are ketogenic, giving rise only to acetylCoA or acetoacetylCoA, neither of which can bring about net glucose production. Ex. Leu and Lys

Glucogenic and Ketogenic aa: Small group of aa comprised of Ile, Phe, Thr, Trp, and Tyr give rise to both glucose and fatty acid precursors and characterized as glucogenic and ketogenic

Sources of Amino Acids

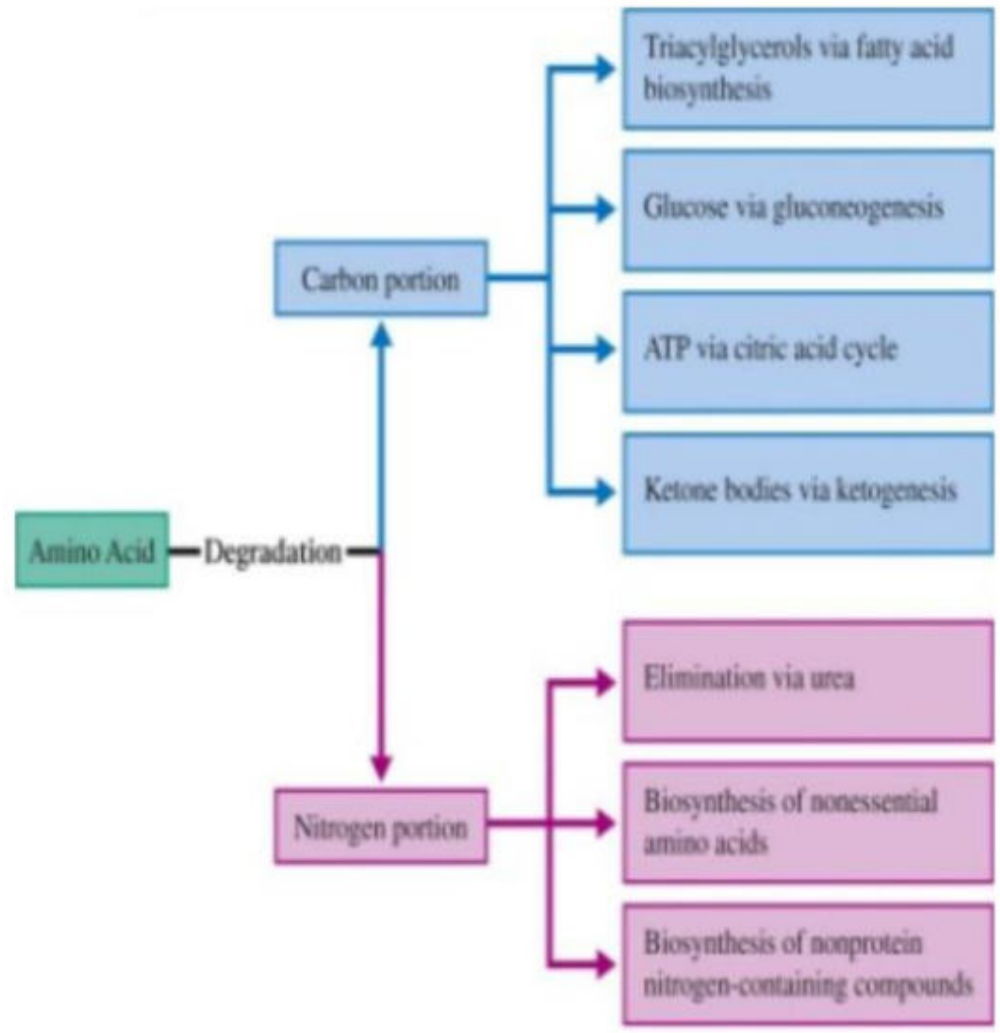
- Ingested dietary proteins is hydrolysed to aa and absorbed from the intestine
- Breakdown of tissue/body proteins
- Glycolysis and citric acid cycle
- Synthesis of non-essential aa

Amino Acid Utilization

Degradation of an aa in two stages:

a) Carbon skeleton, is then converted to pyruvate, acetyl CoA, or citric acid cycle intermediate, depending on its makeup, with the resulting energy production or energy storage

b) Amino nitrogen atom is removed and converted to ammonium ion, which ultimately is excreted from the body as urea.



Nitrogen Balance

Nitrogen balance occurs when synthesis of body protein equals degradation.

- Amount of nitrogen excreted in the urine each day equals the amount of nitrogen ingested each day

Positive nitrogen balance occurs when synthesis of body protein excess compare to degradation.

- Less nitrogen is excreted than ingested (growth, e.g. growing infants and children, pregnant women, tissue repair)

Cont--

Negative nitrogen balance occurs when synthesis of body protein lesser compare to degradation.

- More nitrogen is excreted than ingested (malnutrition, absence of one or more essential aa in diet)
- It occurs in injury, stress response, malnutrition of essential aa

Amino-group metabolism

- α-amino group is the nitrogen source during aa metabolism
- Nitrogen is removed from aa as a ammonia, which needs to be detoxified to urea

Three steps involved in flow of nitrogen from aa to urea:

(1) Transamination (amino group transferred to glutamate),

(2) Oxidative deamination of glutamate (removal of amino group),

(3) Synthesis of Urea

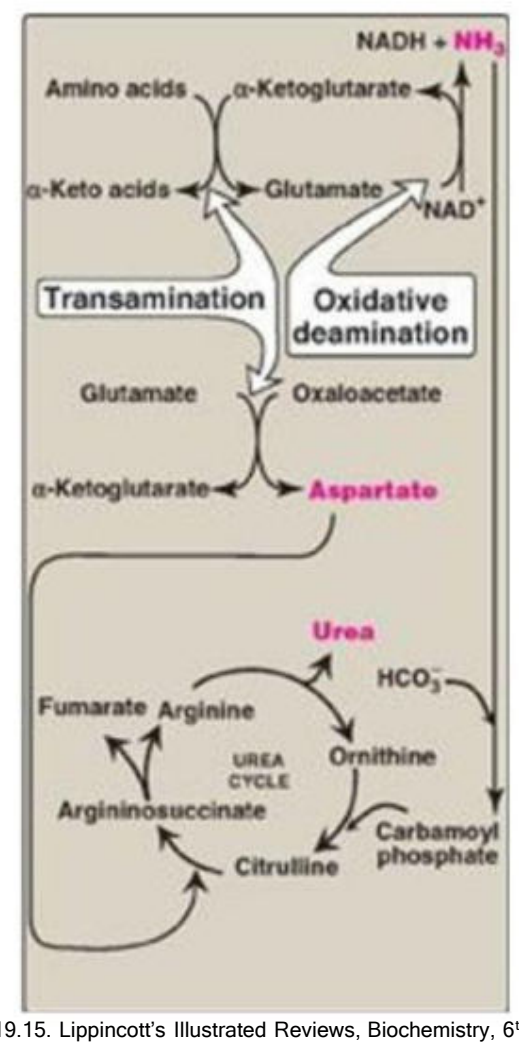
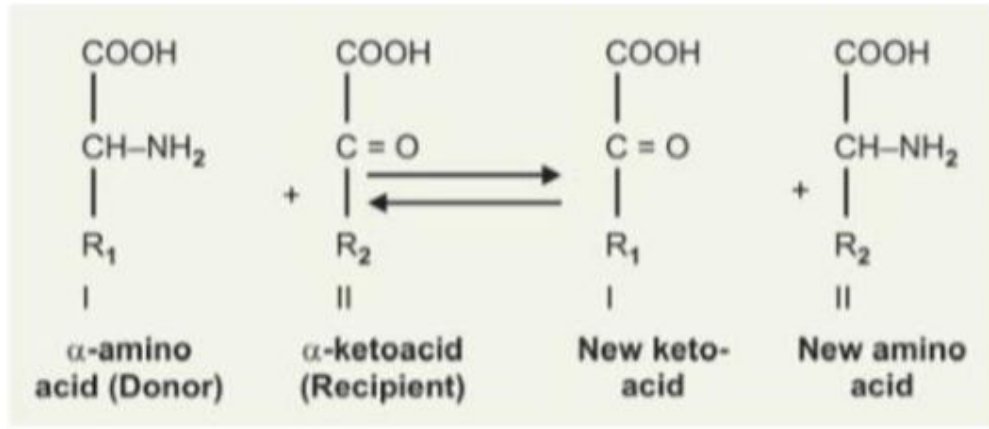


Fig 19.15. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

Transamination

- α-NH2 group of one aa is transferred to a α-ketoacid resulting in formation of a new aa and a new ketoacid

- Donor aa (I) becomes a new ketoacid (I) after losing the α-NH2 group, and recipient ketoacid (II) becomes a new aa (II) after receiving the NH2 group



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- α-amino group from L-amino acid is transferred to α-carbon atom of α-ketoglutarate, produced α-keto acid and glutamate

- Transfer of amino groups from one carbon skeleton to another is catalyzed by aminotransferases

- All aminotransferases have prosthetic group, which is pyridoxal phosphate (PLP), coenzyme form of pyridoxine or vitamin B_6

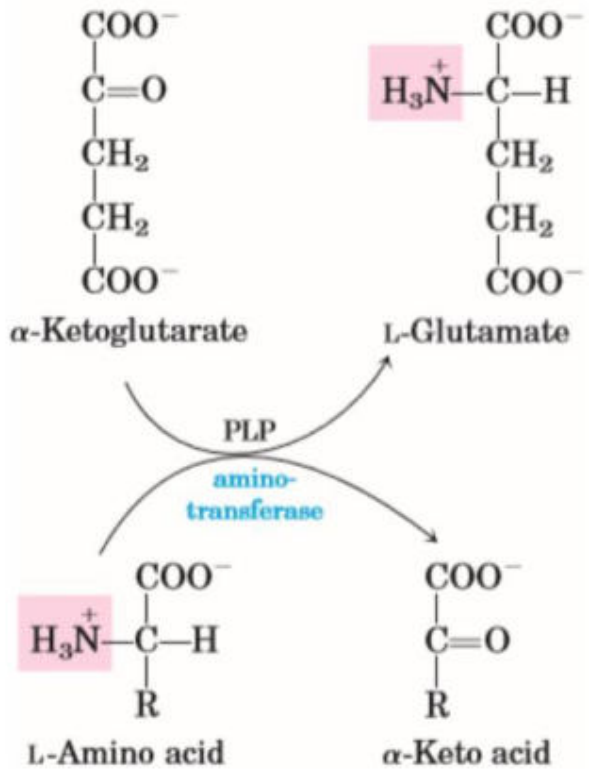

Fig18.4: Lehninger Principles of Biochemistry by David L Nelson

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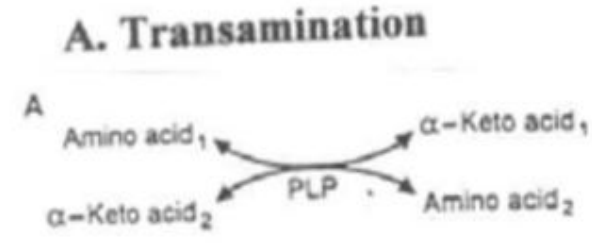
- Transfer of an α-amino group from one aa to an α-keto acid in a reversible reaction
- Location: cytoplasm of all cells
- Enzyme: Transaminases (aminotransferases)



- Co-factor: Pyridoxal phosphate (PLP), derivative of vitamin B_6
- Common donor/acceptor pair: α-ketoglutarate and glutamate

Cont--

- Glutamate then functions as excretion pathways that lead to the elimination of nitrogenous waste products
- All aa except lysine and threonine participate in transamination in their catabolism but they undergo deamination reaction
- Two aminotransferase reactions are catalyzed by alanine aminotransferase (ALT) and aspartate transferases (AST)

Cont--

Alanine aminotransferase

- In this alanine is the donor aa and α-ketoglutarate is the recipient ketoacid resulting in formation of pyruvate and glutamate.
- During amino acid catabolism, this enzyme functions in the direction of glutamate synthesis.

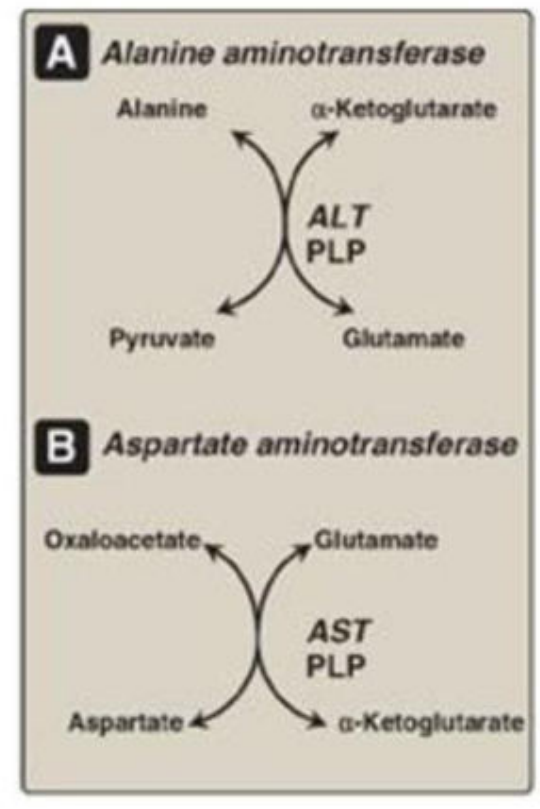


Fig 19.8. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

Aspartate aminotransferase

- In this Aspartic acid is the donor amino acid and α-ketoglutarate is the recipient ketoacid.
- During aa catabolism, this enzyme transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle.

Diagnostic value of plasma aminotransferases

Alanine aminotransferase

- Normal enzyme activity is 3 to 15 IU/L
- It is entirely cytoplasmic
- Increases in viral hepatitis, diabetes, congestive heart failure, liver damage

Aspartate aminotransferase

- Normal enzyme activity is 4 to 17 I.U/L
- It is cytoplasmic and also mitochondrial
- Increases in Liver diseases, muscular dystrophies, acute pancreatitis, leukaemias, acute haemolytic anaemia

Deamination

- In oxidative deamination reactions result in the liberation of the amino group as free ammonia
- Amino groups from many of the α-aa are collected in the liver in the form of the amino group of L-glutamate molecules
- These amino groups must next be removed from glutamate to prepare them for excretion
- In hepatocytes, glutamate is transported from the cytosol into mitochondria, where it undergoes oxidative deamination catalyzed by L-glutamate dehydrogenase

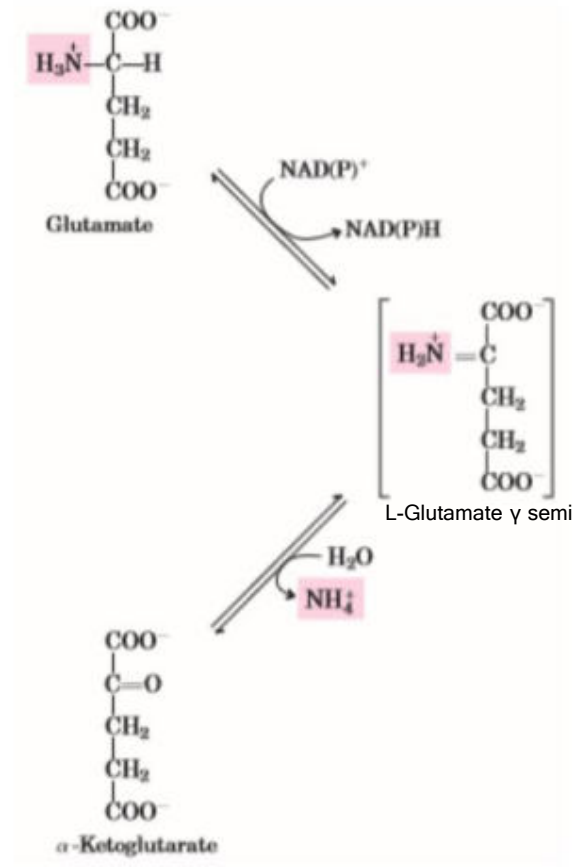


Fig18.7: Lehninger Principles of Biochemistry by David L Nelson

Cont--

- It is the only enzyme that can use either NAD^+ or $NADP^+$ as the acceptor of reducing equivalents
- This oxidative deamination of glutamate is the main mechanism for release of aa nitrogen as ammonia (NH_4^+) in a reversible reaction.
- Location: Mitochondria of hepatocytes
- Allosteric regulation of oxidative deamination: High energy state inhibits the GDH and low energy state stimulates the enzyme.

Transdeamination

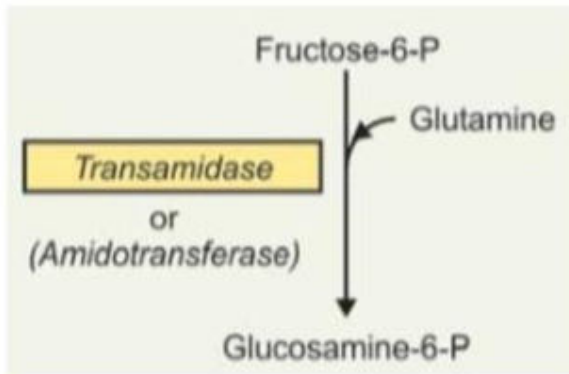
- Transfer of amino nitrogen to α-ketoglutarate forms l-glutamate.
- Hepatic l-glutamate dehydrogenase (GDH), which can use either NAD+ or NADP+, releases this nitrogen as ammonia
- Conversion of α-amino nitrogen to ammonia by the coordinated action of glutamate aminotransferase and GDH is “transdeamination”

Cont--

- Liver GDH activity is allosterically inhibited by ATP, GTP, and NADH, and is activated by ADP
- GDH reaction is freely reversible, and also functions in aa biosynthesis
- The α-ketoglutarate formed from glutamate deamination can be used in the citric acid cycle and for glucose synthesis

Transamidation

- Transamidation involves transfer of -NH2 from a carboxamide group to a suitable acceptor
- Formation of glucosamine-6-P:The amide-N of glutamine can be transferred to a ketogroup
- If transferred to a Keto group of fructose-6-P, it forms Glucosamine-6-P by a transamidation reaction from Glutamine as the 1st step of hexosamine biosynthesis pathway



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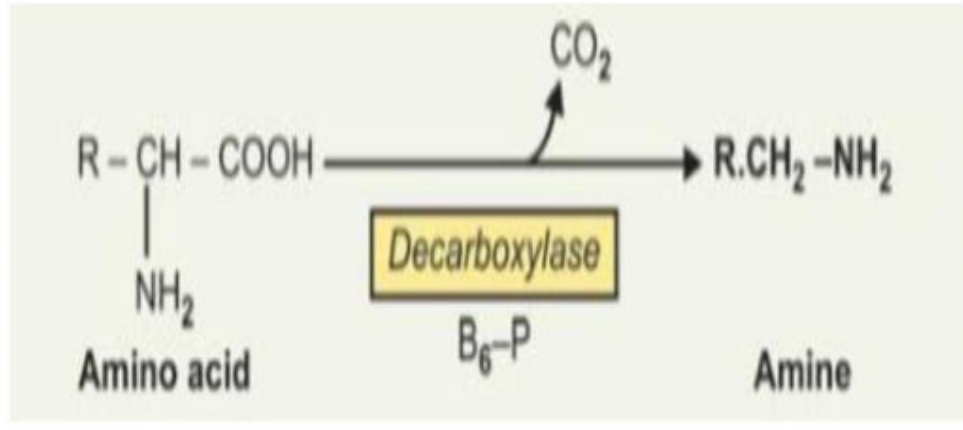
Decarboxylation

- Reaction by which CO2 is removed from the COOH group of an aa as a result an amine is formed
- This reaction is catalysed by decarboxylase, which requires pyridoxal-P (B6-PO4) as coenzyme
- The enzyme removes CO2 from COOH gr. and converts the aa to corresponding amine



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- End-product of this pathway is UDP-GlcNAc, used to make glycosaminoglycans, proteoglycans and glycolipids

- The catalysing enzyme is L-glutamine-D-fructose-6-P transamidase

Cont--

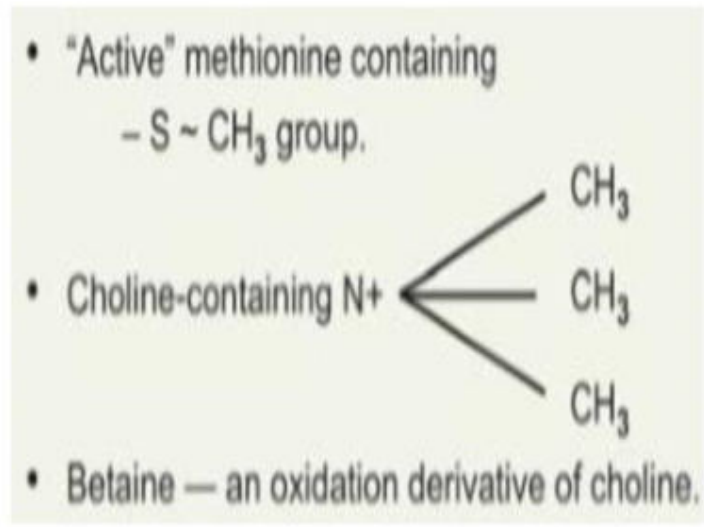
- This is mostly a process confined to putrefaction in intestines and produces amines

- Ex. Threonine is converted into Propanol amine (Constituent of Vit B_{12})

- Isoleucine undergoes transamination, followed by oxidative decarboxylation of resulting α-keto acid

Transmethylation

- Transmethylation Certain compounds of the body, with structures containing CH3 group attached to an atom other than carbon can take part in enzymatic reactions
- Whereby these -CH3 groups are transferred to a suitable “acceptor”, which have no -CH3 group



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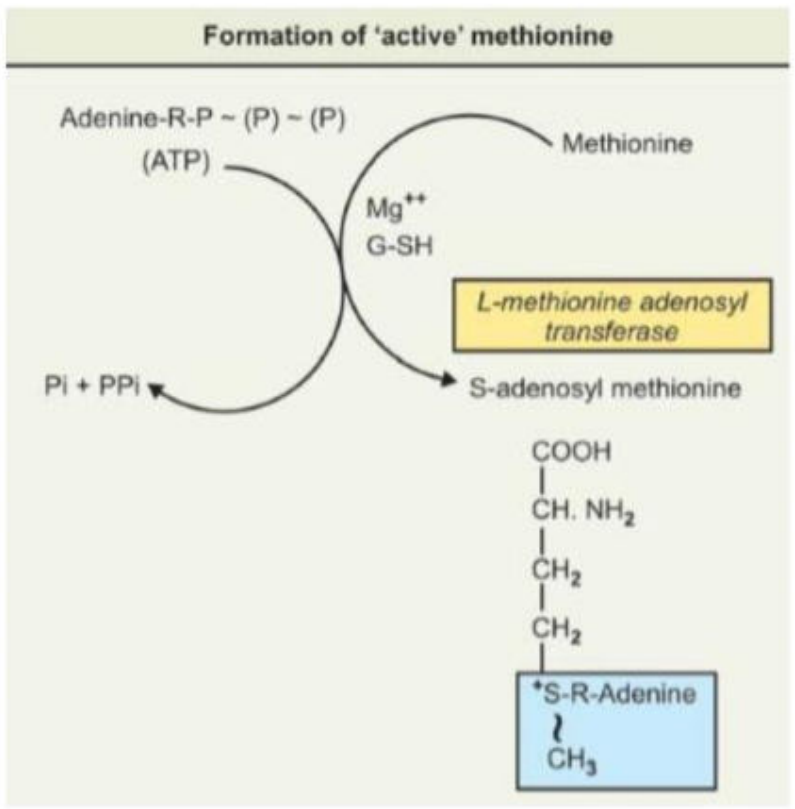
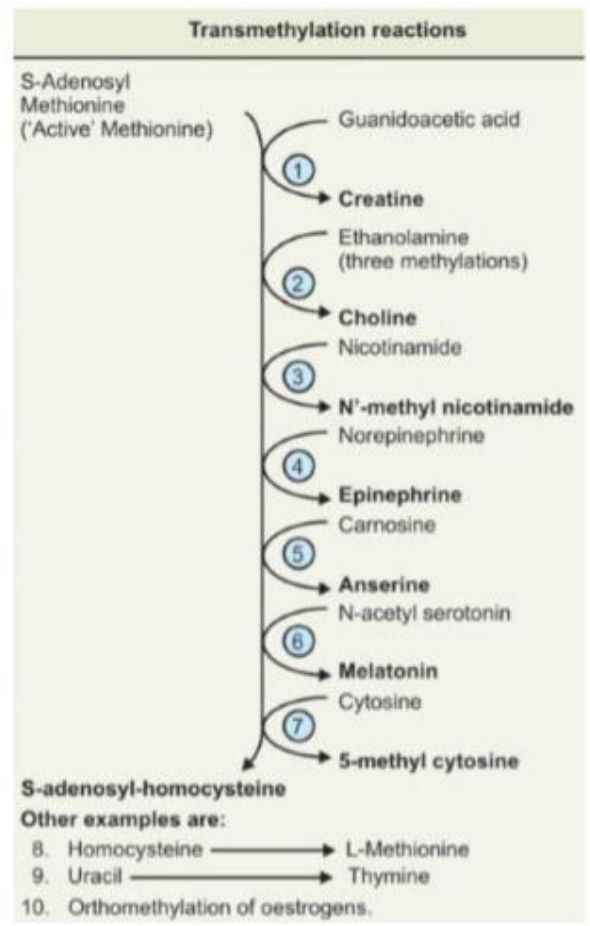
Cont--

- Such reactions are termed as “transmethylation reaction”, and the substrate, i.e. the -CH3 donor is said to possess biologically labile -CH3 group”
- Most important compounds with biologically labile methyl group are active methionine

Transmethylation reactions





Text Book of Medical Biochemistry by Chatterjee & Rana Shinde, 8th Ed

Group Discussion

- Subtopics of previous class discussed in groups.

Reference Books

1) Text Book of Medical Biochemistry by Chatterjee & Rana Shinde, 8th Ed
2) Biochemistry, Lippincott's Illustrated Reviews, 6th Ed
3) Harper's Illustrated Biochemistry-30th Ed
4) Lehninger Principles of Biochemistry

Thank you