Amino-acid Oxidation

Department of Biochemistry

Specific Learning Objectives

- Fates of Amino Acids
- Amino Acid Utilization
- Amino-group metabolism
- Explain role of transamination reactions in aa synthesis and identify vitamin essential for this reaction (tie in to urea cycle)
- Describe interconversion between ketoacids and aa, including requirement of pyridoxal phosphate (PLP) as a cofactor
- Outline formation and transport of ammonia
- Describe importance of reactions catalyzed by glutamine synthetase, glutaminase, and glutamate dehydrogenase
- Ammonia Intoxication
- List causes for hyperammonemia, its consequences, and treatments to reduce blood ammonia levels

Overview of AA catabolism

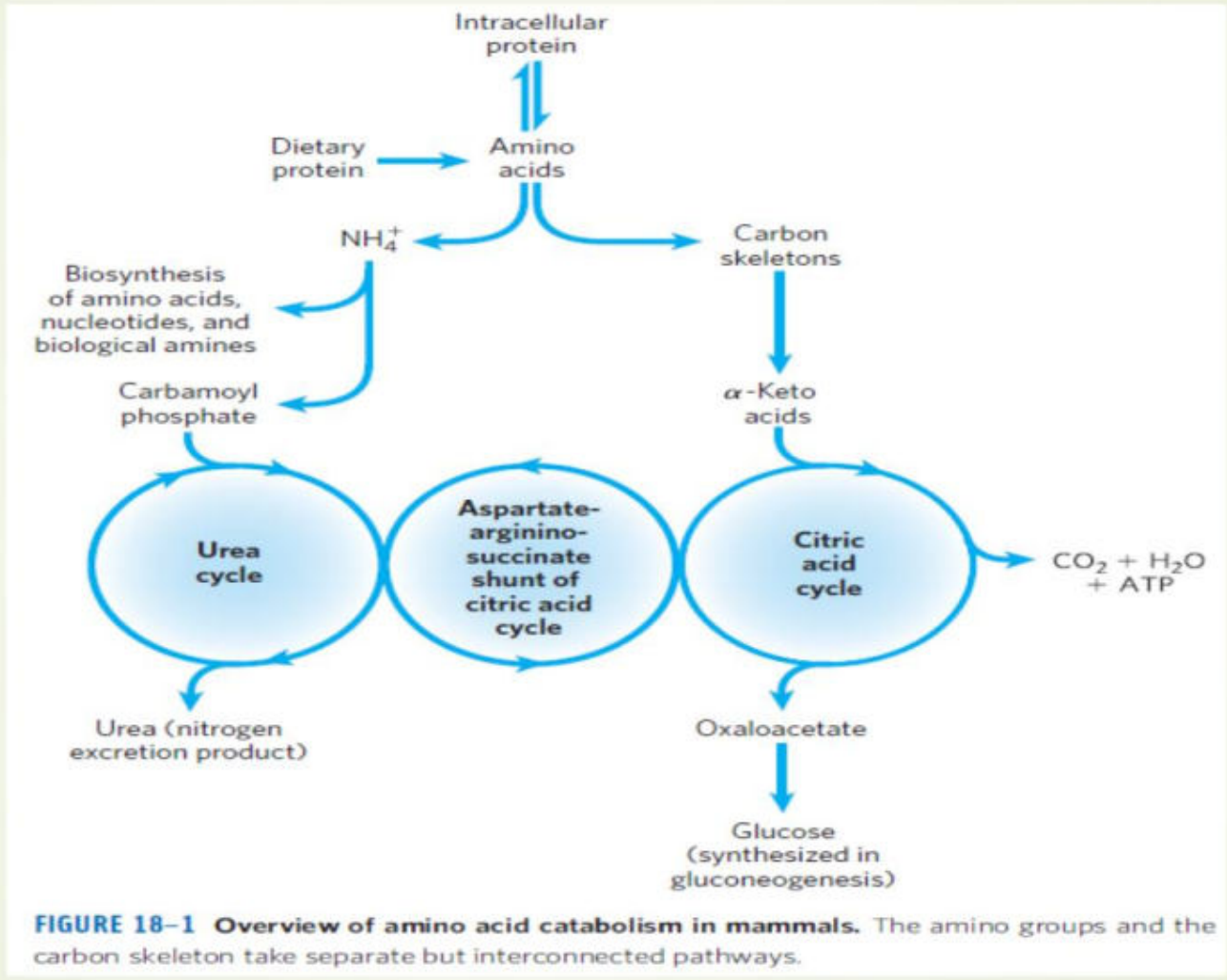

FIGURE 18–1 Overview of amino acid catabolism in mammals. The amino groups and the carbon skeleton take separate but interconnected pathways.

Fig18.1: Lehninger Principles of Biochemistry by David L Nelson, 6th Ed

Amino Acid oxidative degradation

It occurs in three metabolic circumstances:

1. During normal synthesis and degradation of Proteins (Protein turnover)

- Some aa released from proteins breakdown and not needed for new protein synthesis

2. If diet is rich in protein and ingested aa exceeds the body needs for protein synthesis, in this case surplus catabolized

2. During starvation or in uncontrolled diabetes, when carbohydrates either unavailable or not properly utilized, in this case cellular proteins are used as a fuel

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Under all above conditions, aa lose their amino groups to form α-keto acids and also form carbon skeletons of aa:

- α-keto acids undergo oxidation to CO_2 and H_2O
- 3-4 carbon units its converted into glucose by gluconeogenesis, fuel for brain, skeletal muscel and other tissues

- Four aa plays imp role in nitrogen metabolism: Glutamate, Glutamine, (both converted to α-ketoglutarate), Alanine (to pyruvate) and Aspartate (to oxaloacetate)

Fates of Amino Acids

- For Protein synthesis
- For synthesis of other nitrogen containing compounds (heme, creatine, purines, pyrimidines, choline, neurotransmitters)
- For 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

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Ketogenic aa: Lysine and leucine are only aa are ketogenic, give rise to acetyl-CoA or acetoacetyl-CoA, neither of which can bring about net glucose production

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

Steps for Amino group catabolism

- In cytosol of liver cells, amino groups from most aa transferred to α-ketoglutarate to form glutamate, which enters mitochondria and gives up its amino group to form ammonia
- Excess ammonia generated in most tissues converted to amide nitrogen of glutamine, which passes to liver, then into liver mitochondria
- In skeletal muscle, excess amino groups are transferred to pyruvate to form alanine
- Aspartate come into play in metabolic processes that occur once amino groups delivered to liver

Amino group catabolism

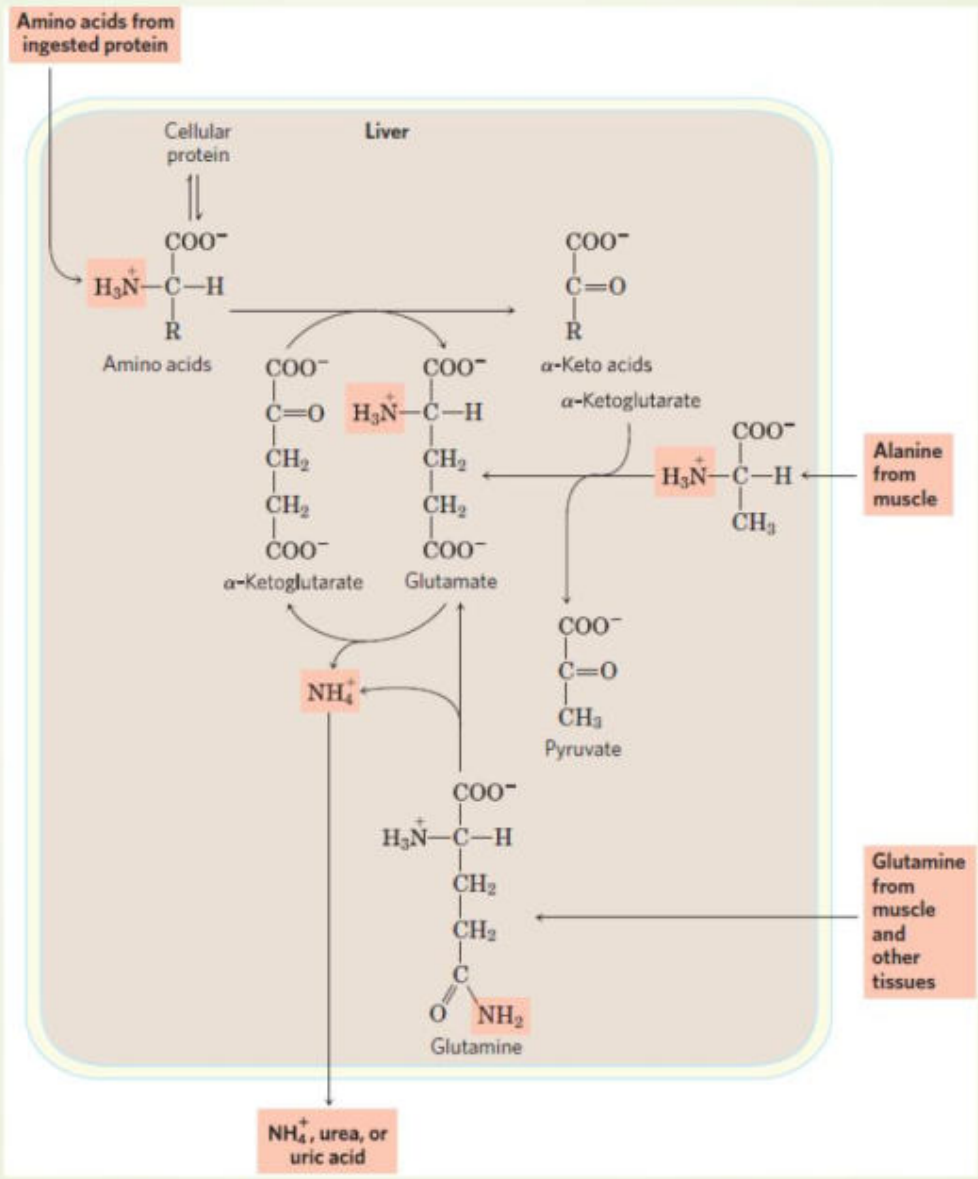


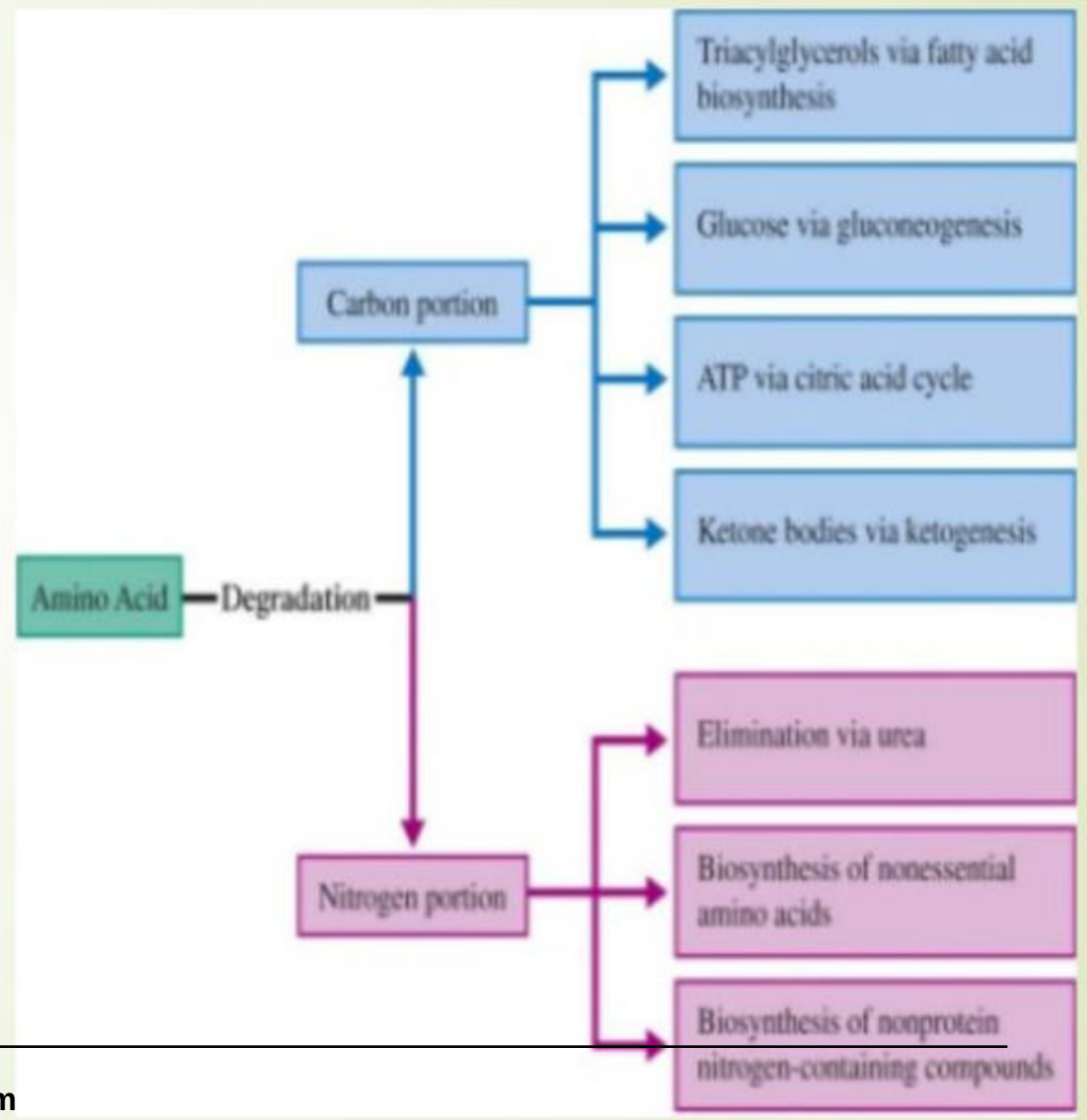
Fig18.2 (a): Lehninger Principles of Biochemistry by David L Nelson, 6th Ed

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 resulting energy production or energy storage

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



Amino-group metabolism

- α-amino group is 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

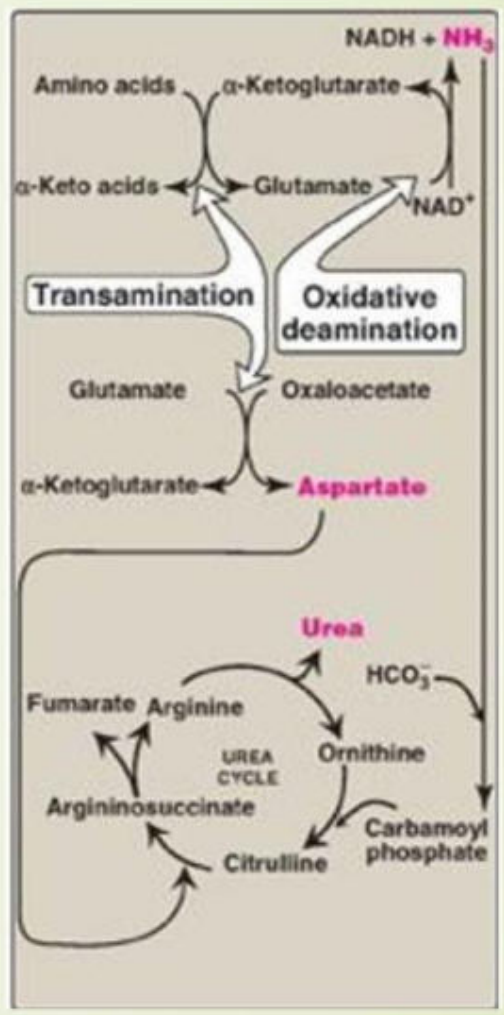
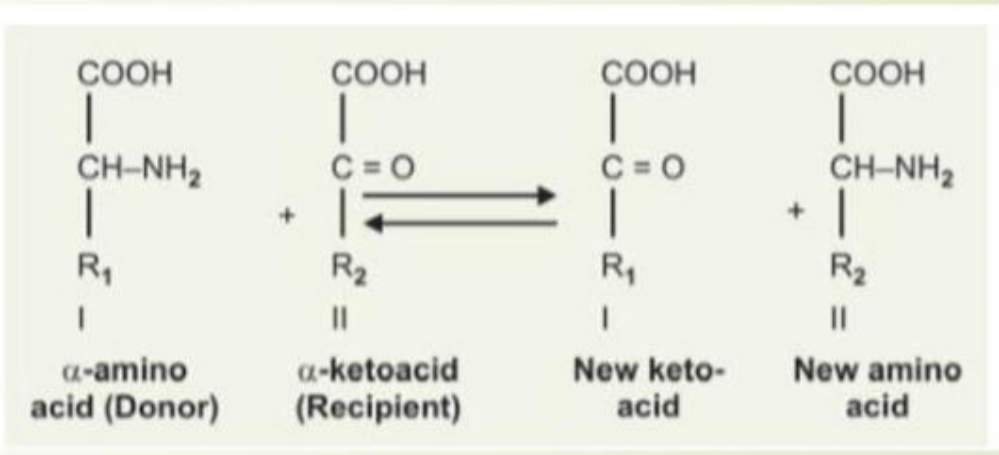


Fig 19.15. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

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



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

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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

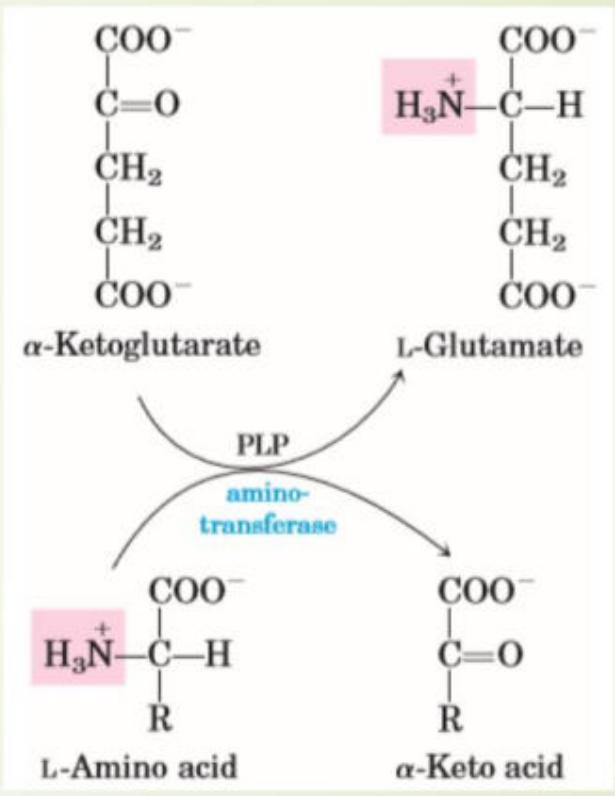

Fig18.4: Lehninger Principles of Biochemistry by David L Nelson

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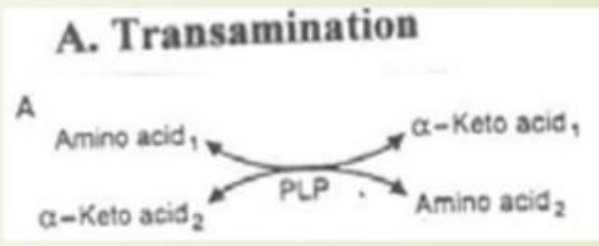
- PLP participates in transfer of α-amino groups to α-ketoglutarate
- Location: cytoplasm of all cells
- Enzyme: Transaminases (aminotransferases)
- Co-factor: Pyridoxal phosphate (PLP), derivative of vitamin B_6
- Common donor/acceptor pair: α-ketoglutarate and glutamate



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- Glutamate function as excretion pathways that lead to 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)

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Alanine aminotransferase: In this alanine is donor aa and α-ketoglutarate is recipient ketoacid resulting in formation of pyruvate and glutamate.

- During aa catabolism, this enzyme functions in direction of glutamate synthesis.

Aspartate aminotransferase: In this Aspartic acid is donor aa and α-ketoglutarate is 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 urea cycle.

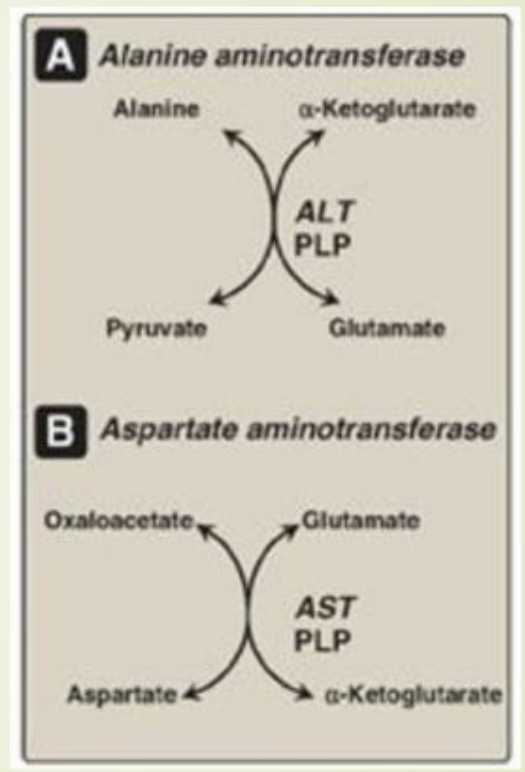

Fig 19.8. Lippincott's Illustrated Reviews, Biochemistry, 6th Ed

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

Oxidative Deamination

- Glutamate releases its amino group as ammonia in Liver

- Amino groups from many of α-aa are collected in liver in form of 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 cytosol into mitochondria, where it undergoes oxidative deamination catalyzed by L-glutamate dehydrogenase

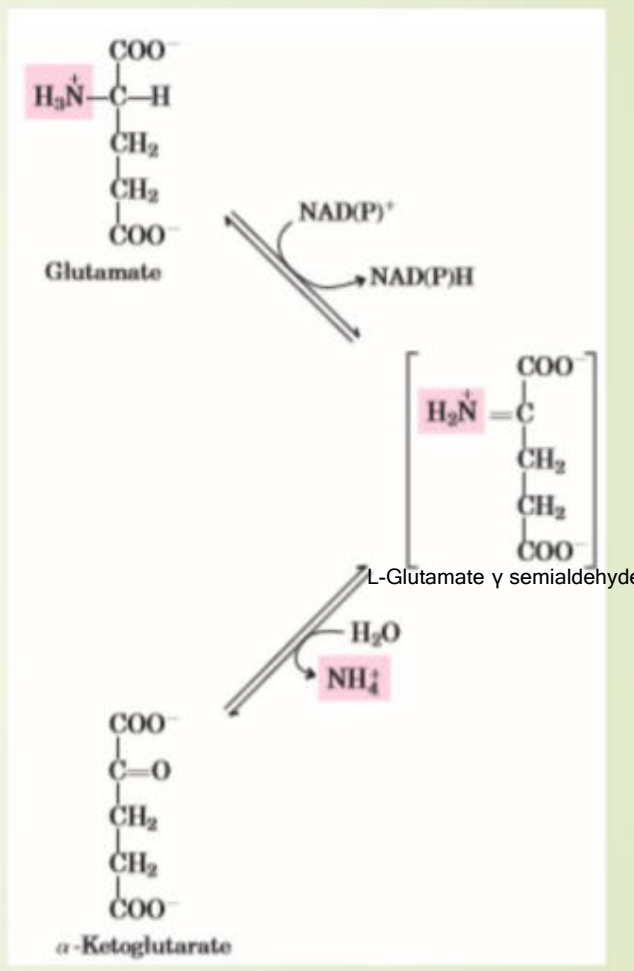

Fig18.7: Lehninger Principles of Biochemistry by David L Nelson, 6th Ed

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- It is only enzyme that can use either NAD_+ or $NADP_+$ as acceptor of reducing equivalents
- Oxidative deamination of glutamate is 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 GDH and low energy state stimulates enzyme.

Transdeamination

- Transfer of amino nitrogen to α-ketoglutarate forms l-glutamate by glutamate aminotransferases
- Hepatic l-glutamate dehydrogenase (GDH), which can use either NAD+ or NADP+, convert glutamate to α-ketoglutarate, releases this nitrogen as ammonia, this α-ketoglutarate used in TCA cycle and glucose synthesis
- Conversion of α-amino nitrogen to ammonia by coordinated action of glutamate aminotransferase and GDH is “transdeamination”

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- 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
- α-ketoglutarate formed from glutamate deamination can be used in citric acid cycle and for glucose synthesis

Clinical-cases discussed

Thank you