AMINO ACID METABOLISM

→ Amino acids not stored

Amino Acids

Diet | Denovo synthesis | Protein Degradation

* Excessive Amino acids lead to catabolism/ Degradation - Steps:

1- Transamination (Removal of $-NH_2$)

2- Oxidative deamination →

Products: 1- Ammonia (urine, urea)

2- α- Keto acid → (form one of the 7 intermediary products)

* Nitrogen enter body through diet

Nitrogen leave body through ammonia, urea, creatinine

* Protein Turnover : Synthesis = Degradation

* Short lived proteins → Regulatory protein and misfolded proteins

* Long Lived proteins → collagen

* Protein Degradation may be ATP dependent proteasome system of cytosol or ATP independent Degradative Enzyme System of Lysosome.

* Lysosome breaks down protein non-selectively through acid hydrolase

PROTEASE SYSTEM

→ ATP dependent Ubiquitin-protease system of the cytosol

→ ATP dependent

⇒ acts selectively on proteins

Step 1: bonding b.w carboxyl group of Glycine of Ubiquitin and amino group of Lysine of cellular protein with the help of 3 enzymes

- E_1 → activate inactivated ubiquitin and transfer it to E_2
- E_3 → Recognize protein and attach to ubiquitin

* Protein-ubiquitin complex recognized by Proteolytic complex called proteasome. ~~protease system~~. Here ubiquitin is removed and protein is degraded.

PEST sequences (Proline, Glutamate, Serine, Threonine)

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Argine, PEST Alanine are destabilizing agents

* Proteins ready for degradation have arginine or posttranslationally modified amino acids such as acetylated alanine on N-terminal end.

* Serine on N-terminal end marks amino acid as stable

* E_1 : Activating enzyme → activates Ubiquitone

* E_2 : Conjugating Enzyme

* E_3 : Ligase → identifies protein to be degraded

* Transamination → Transfer of amino groups from most amino acids to α-Ketoglutarate to produce glutamate

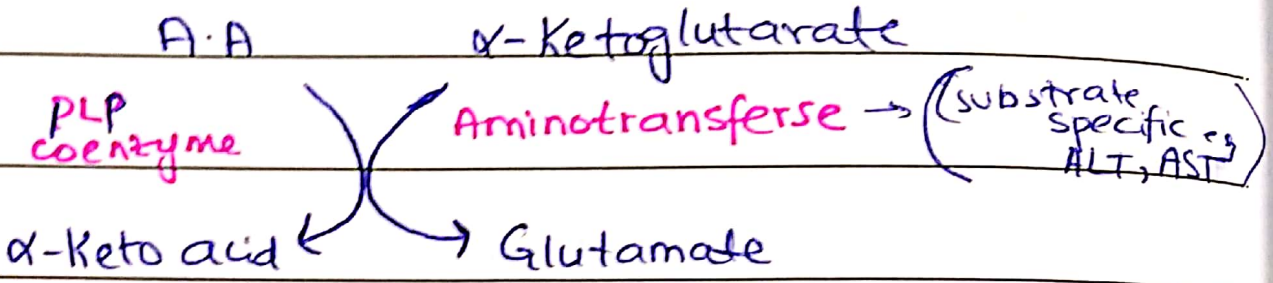
* Oxidative Deamination of Glutamate, thereby regenerating α-Ketoglutarate

AMINO ACID CATABOLISM

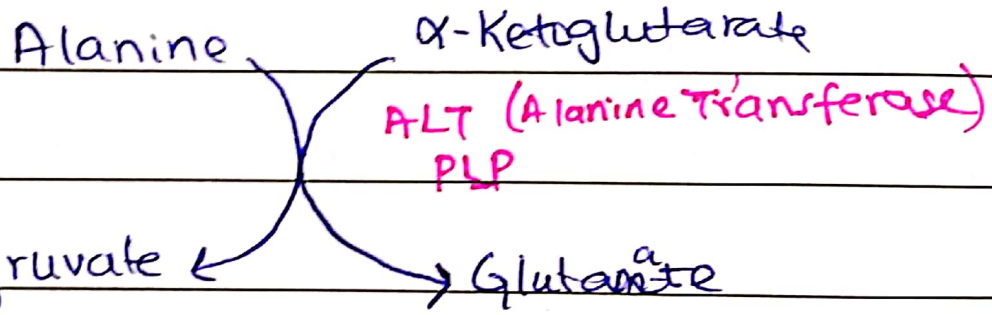
Catabolism: (1) Transamination

(2) Oxidative deamination

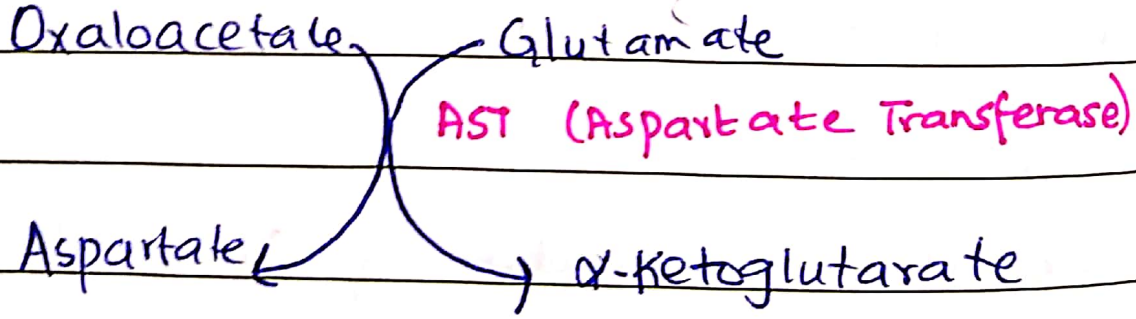
(1) Transamination: Removal of $-NH_2$ from A.A



eg)



Example (2)



* All amino acids except lysine and threonine participitate in trans amination at some point in their catabolism

ALT	AST
(1) Alananine	(1) For Aspartat
(2) Favors Glutamate synthesis	(2) Glutamate breakdown - Aspartate synthesis

(3) Both present intracellularly & so elevated levels of these enzymes in plasma may indicate cell injury.

- In hepatic cases → ALT more specific for injury while AST more sensitive for injury

* Plasma AST and ALT are elevated in nearly all hepatic diseases but are particularly high in conditions that cause extensive cell necrosis, such as severe viral hepatitis, toxic injury, and prolonged circulatory collapse.

DAO : De Amino Acid Oxidase

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L-Amino Acid Oxidase found in Snake Venom

(2) OXIDATIVE DEAMINATION

Glutamate

NAD ⇄ NADPH

NH_3 →

Glutamate Dehydrogenase (GDH) (coenzyme NAD)

NAD → NADH

→ NH_3 ---- transported to liver

α-Ketoglutarate

* Two Allosteric Regulators of GDH

1- GTP (−)

2- ADP (+)

* D-Amino Acid Oxidase (DAO)

D-Amino Acid (from diet)

↓ FAD-dependent DAO → in the peroxisome of Liver and Kidney cells

α-Keto acid, NH_3, H_2O_2

- Increased DAO activity has been linked to increased susceptibility to Schizophrenia

* Ammonia Transport to Liver

↳ Ammonia transported from peripheral tissues to liver for conversion into urea.

Muscle: Glutamate

NH_3 → Glutamine synthetase

Glutamine

Liver

Glutamine → Glutaminase → Glutamate + NH_3 → α-Ketoglutarate + NH_3

* One Nitrogen of urea molecule is supplied by free ammonia and the other nitrogen by Aspartate.

Glutamate is immediate precursor of both ammonia and aspartate nitrogen.

Urea: NH_2 $C=O$ NH_2

UREA CYCLE

1. C from HCO_3^-
2. N from NH_3
3. 2 ATP used

CPS-I Regulator: N-Acetyl Glutamate (+)

- C + N + 2ATP —CPS-I (Rate Limiting Step)→ Carbomyl Phosphate
- Carbomyl Phosphate + Ornithine

In mitochondria

↓

L-citruline

↓ cytosol

L-citruline + Aspartate (provide N)

ATP → Ariginosuccinate Sythetase

Urea is produced by liver and then transported in blood to kidneys for excretion in urine.

↓

Arginosuccinate

Arginossuccinate Lyase

↓ ↓

Fumarate → Malate → OAA → Aspartate

Arginine —Arginine-I→ Urea + Ornithine

METABOLISM OF α-KETO ACIDS

* Seven intermediary products of α-Keto acids

1. Oxaloacetate → Aspargine
2. Pyruvate
3. α-Ketoglutarate
4. Fumarate
5. Succinyl CoA
6. Acetyl-CoA
7. Acetoacetate

* Glucogenic Amino acids : α-Keto acids upon breakdown produce intermediates which are substrates for gluconeogenesis
* Ketogenic Amino acids : yield either acetoacetate or one of its precursors.

Leucine and Lysine are exclusively ketogenic

* Both Glucogenic and Ketogenic : TTIP

Tyrosine
Tryptophan
Isoleucine
Phenylalanine

* Amino Acids producing Oxaloacetate:

→ Aspargine

* A.A producing α-Ketoglutarate (GAPH)

→ Glutamine

→ Proline

→ Arginine

→ Histidine

* A.A producing Pyruvate

→ Alanine → Glycine

→ Serine

→ Cysteine

→ Threonine

* A.A producing Fumarate

→ Phenylalanine

→ Tyrosine

* A.A forming Succinyl CoA

→ Methionine

- A.A forming Succinyl CoA
  - → Valine
  - → Isoleucine
  - → Threonine
- A.A forming Acetyl CoA or Acetoacetyl CoA
  - → Tryptophan
  - → Leucine
  - → Isoleucine
  - → Lysine

BIOSYNTHESIS OF NON-ESSENTIAL AMINO ACIDS

→ Synthesis from

(1) SYNTHESIS FROM α-KETO ACIDS

Pyruvate → (NH2) → Alanine

OAA → (NH2) → Aspartate

α-Ketoglutarate → (NH2) → Glutamate

(2) SYNTHESIS FROM AMMONIA

Glutamate → (NH_3, ATP) → Glutamine

Aspartate → (NH_3 from Glutamine, ATP) → Asparagine

+ SYNTHESIS OF PROLINE

Glutamate

↓

Glutamate Semi Aldehyde

↓

Proline

SERINE

3-Phospho Glycerate OR Glycine

↓ ↓

3-Phospho pyruvate Serine

↓

3-Phospho serine

↓

Serine

CYSTEINE

Methionine

↓

S-Adenosyl Methionine (SAM)

↓

S-Adenosyl homocysteine (SAH)

↓

Homocysteine

↓

Cystathion

↙ ↘

Cysteine α-Ketobutyrate

✱ TYROSINE

Phenylalanine

↓

Tyrosine

✱ SOME IMPORTANT AMINO ACIDS

- Methionine precursor of cysteine
- Phenylalanine precursor of Tyrosine
- Arginine component of urea cycle
- Arginine precursor of nitric oxide
- Histidine precursor of histamine
- Tryptophan precursor of serotonin
- Glutamine → storage and transport form of ammonia
- Glutamine precursor of purines and pyrimidines
- Alanine → transport form of ammonia from muscle
- Alanine key glucogenic amino acid

LIPINCOTT

* In The inherited disorder, cystinuria, The carrier system for absorption of cystine, ornithine, arginine and Lysine (COAL) is defective and all four amino acids appear in The urine

* CPS-I required in urea cycle.
CPS-II required for biosynthesis of pyrymidines

* Arginine-I required in urea cycle to cleave Arginine into urea and ornithine

* Arginine-II in kidneys control arginine availability for nitric oxide synthesis

* Ammonia Obtained From:

1- Glutamine

2- Analine

3. Intestinal bacteria

4. Amines obtained from diet

5- Monoamines that serve as hormones or neurotransmitters

6. From catabolism of purines and pyrimidines

AMMONIA TRANSPORT TO LIVER

1- By Glutamine

2- By Alanine

(1) BY GLUTAMINE

Glutamate

↓ Glutamine Synthetase

Glutamine

↓ carried to Liver

Glutamine

↓ Glutaminase

Glutamate + NH_3

↓ GDH

α-Ketoglutarate + NH_3

- NH_3 → Urea

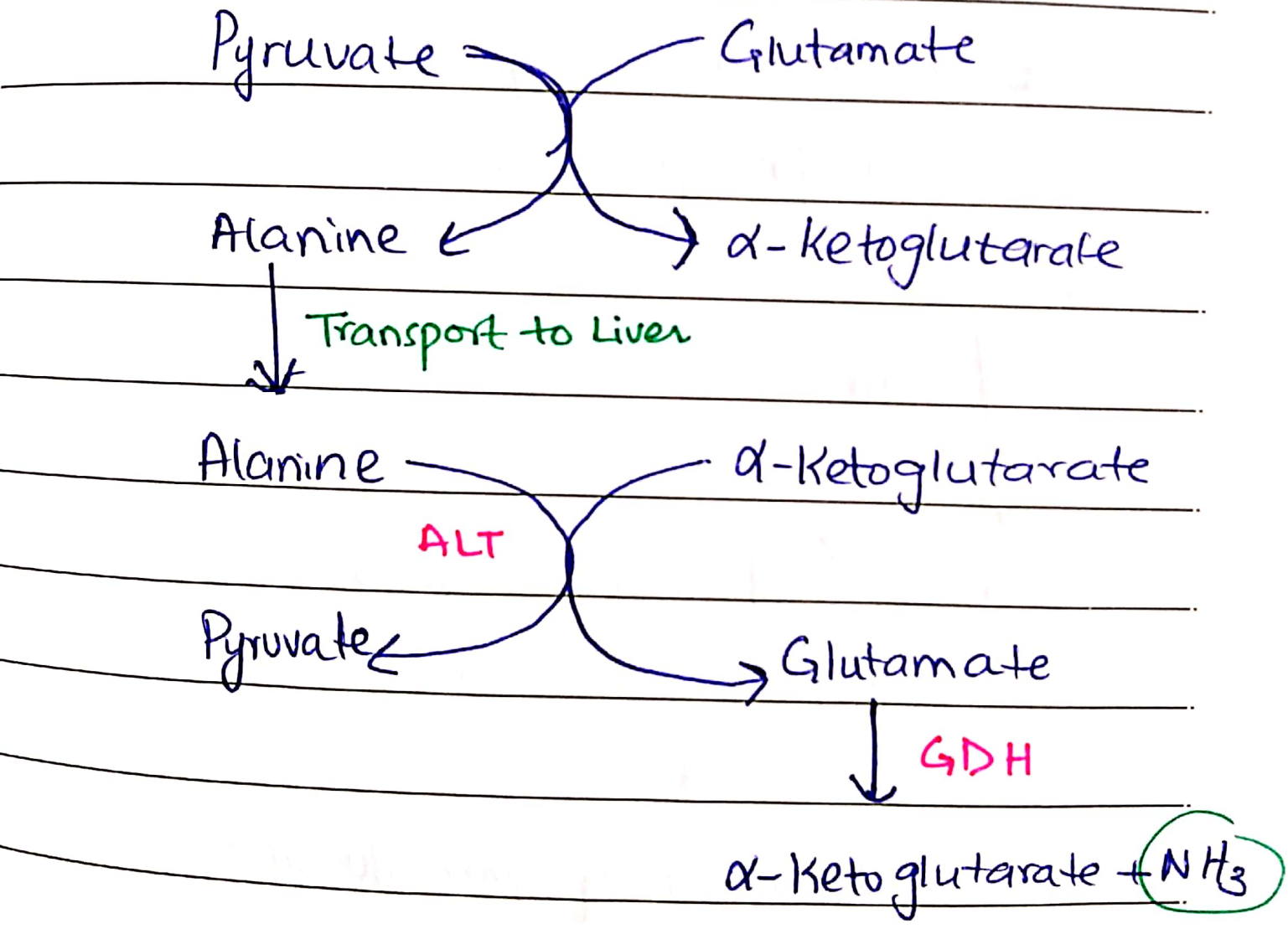
② BY ALANINE

Isoleucine, Valine

↓

Succinyl CoA

↓



* Cysteine can be oxidized to its disulfide derivative, cystine.

PHENYLKETONURIA (PKU)

→ caused by deficiency of phenylalanine hydroxylase

→ Characterized by hyperphenylalaninemia (excess phenylalanine)

Phenylalanine (excess in PKU)

↓ PAH

Tyrosine (deficient in PKU)

→ deficiency of neurotransmitters such as serotonin and catecholamines

→ elevated levels of phenylketone in the urine (hence name phenylketonuria)

→ urine having characteristic musty (mousy) odour

→ hypopigmentation (as tyrosine is required for production of melanin)

→ Treatment of PKU must begin during the first 7-10 days of life to prevent cognitive impairment

→ High blood phenylalanine in pregnant mother has a teratogenic effect, causing microcephaly and congenital heart abnormalities in the fetus.

MAPLE SYRUP URINE DISEASE

→ rare autosomal recessive disorder

→ partial or complete deficiency in BCKD, the mitochondrial enzyme complex that oxidatively decarboxylates leucine, isoleucine and valine.

→ Maple syrup like odour of urine bcz of rise in isoleucine

→ Elevated leucine is cause of neurologic damage

→ Symptoms : Feeding problems, vomiting, ketoacidosis, changes in muscle tone, neurologic problems that result in coma

* ALBINISM

→ A defect in Tyrosine metabolism resulting in deficiency in production of melanin

→ Hypopigmentation, vision Defects and photophobia (sunlight hurt their eyes)

→ Increased risk of skin cancer

* HOMOCYSTINURIA

→ Defects in metabolism of homocysteine

→ High urinary levels of Hcy, high plasma levels of Hcy and methionine, low plasma levels of cysteine.

→ Most commonly: Defect in enzyme cystathione β-synthase

ALKAPTONURIA

→ Rare organic aciduria

→ Deficiency of homogentistic acid oxidase resulting in accumulation of homogentistic acid, an intermediate in the degradative pathway of Tyrosine