METABOLISM OF AMINO ACIDS

assistant professor Dr. Abdulhussien M. Aljebory
College of pharmacy
Babylon University
1. Introduction
2. Amino acid classification
3. Some definitions:
   - nitrogen balance (NB)
   - protein requirement
   - biological value (BV)
4. Digestion of protein
5. Absorption of protein
6. Metabolic fate of protein
7. Metabolism of amino acids:
   - removal of ammonia: by deamination, transamination and transdeamination
   - fate of carbon skeletons of amino acid
   - metabolism of ammonia
Protein Metabolism

• Non-essential amino acids can be formed by **transamination**, transfer of an amine group to keto acid. Can also be eaten.

• If used for energy, amino acids undergo **oxidative deamination**. Ammonia and keto acids are produced as by-products of oxidative deamination. Ammonia is converted to urea and excreted.

• Amino acids are not stored in the body
*Metabolism of proteins is the metabolism of amino acids.

*Metabolism of amino acids is a part of the nitrogen metabolism in body.

*Nitrogen enters the body in dietary protein.

*Dietary proteins cannot be stored as such but used for formation of tissue proteins due to there is a continuous breakdown of endogenous tissue proteins.
Essential amino acids:
Lysine, Leucine, Isoleucine, Valine, Methionine, Phenylalanine, Threonine, Tryptophan

Nonessential amino acids:
Alanine, glycine, aspartate, glutamate, serine, tyrosine, cysteine, proline, glutamine, aspargine

Histidine & arginine are semi essential. They are essential only for infants growth, but not for old children or adults where in adults histidine requirement is obtained by intestinal flora & arginine by urea cycle.

For formation of new tissue protein:
all essential amino acids that can not be synthesized by organism & provided by dietary protein must be present at the same time with nonessential amino acids that can be synthesized by organism
Nitrogen Balance (NB):

- **Nitrogen balance** is a comparison between **Nitrogen intake** (in the form of dietary protein) and **Nitrogen loss** (as undigested protein in feces, NPN as urea, ammonia, creatinine & uric acid in urine, sweat & saliva & losses by hair, nail, skin).

- NB is important in defining
  1. overall protein metabolism of an individual
  2. nutritional nitrogen requirement.
Three states are known for NB:

a) **Normal adult:** will be in nitrogen equilibrium, 
   Losses = Intake

b) **Positive Nitrogen balance:**
   Nitrogen intake *more* than losses *(High formation of tissue proteins)* occurs in growing children, pregnancy, lactation and convulascence.

C) **Negative Nitrogen balance:**
   Nitrogen losses *more* than intake occurs in:- *(Low intake of proteins)* in starvation, malnutrition, GIT diseases
   - *(High loss of tissue proteins)* in wasting diseases like burns, hemorrhage & kidney diseases with albuminurea
   - *(High breakdown of tissue proteins)* in **D.M., Hyperthyroidism, fever, infection**
Protein Requirement for humans in Healthy and Disease Conditions

The normal **daily requirement of protein** for adults is $0.8 \text{ g/Kg body wt. day}^{-1}$.

- That requirement is **increased** in **healthy** conditions: during the periods of rapid growth, pregnancy, lactation and adolescence.
- Protein requirement is **increased** in **disease** states: illness, major trauma and surgery.
- Req. for protein should be **reduced** in: hepatic failure and renal failure.
Biological Value for Protein (BV):

* **BV** is: a measure for the ability of dietary protein to provide the **essential amino acids** required for tissue protein maintenance.

* Proteins of **animal sources** (meat, milk, eggs) have **high** BV because they contain **all** the **essential amino acids**.

* Proteins from **plant sources** (wheat, corn, beans) have **low** BV thus combination of **more than one** plant protein is required (**a vegetarian diet**) to increase its BV.
DIGESTION OF PROTEIN

• Proteins are broken down by hydrolyases (peptidases or proteases):
  • **Endopeptidases** attack internal bonds and liberate large peptide fragments (pepsin, trypsin, Chymotrypsin & Elastase)
  • **Exopeptidases** remove one amino acid at a time from –COOH or –NH₂ terminus (aminopeptidase & carboxypeptidase)

• Endopeptidases are important for initial breakdown of long polypeptides into smaller ones which then attacked by exopeptidases.

• Digestion of protein can be divided into: a gastric, pancreatic and intestinal phases.
I. Gastric Phase of Protein Digestion: (represents 15% of protein digestion)

1) **Pepsin**: in adult stomach, secreted as pepsinogen. It is specific for peptide bond formed by aromatic or acidic amino acids.

2) **Rennin**: in infants for digestion of milk protein (casein).
II. Pancreatic Phase of Protein Digestion

- This phase ends with **free amino acids** and **small peptides** of 2-8 amino acid residues which account for 60% of protein digestion.
III. Intestinal Phase of protein digestion:

- Intestinal enzymes are:
  aminopeptidases (attack peptide bond next to amino terminal of polypeptide) & dipeptidases
- The end product is free amino acids dipeptides & tripeptides.
Absorption of Amino Acids and Di- & Tripeptides:
Absorption of Amino Acids and Di- & Tripeptides:

*L-amino acids* are **actively** transported across the intestinal mucosa (need carrier, Na\(^+\) pump, Na\(^+\) ions, ATP).

**Different carrier transport systems are:**

a) For **neutral** amino acids.

b) For **basic** amino acids and **cysteine**.

c) For **imino acids** and **glycine**.

d) For **acidic** amino acids.

e) For **B-amino acids** (B-alanine & taurine).

*D-isomers* transported by **simple** diffusion.
The transcellular movement of amino acids in an intestinal cells:

Amino acid (Symport) Na+

Amino acid Na+ (Antiport)

Lumen Cytosol Extracellular fluid

K+ K+
Tri- & Dipeptides can actively transported faster than their individual amino acids.

intact proteins:

1. Immunoglobulins of colostrum are absorbed by neonatal intestines through endocytosis without loss of their biological activity and thus provide passive immunity to the infants.

2. Vaccines (undigested polypeptides) in children and adults are absorbed without loss of their biological activity producing antigenic reaction and immunologic response.
METABOLIC FATES OF AMINO ACIDS:

1- Body **protein** biosynthesis.
2- Small **peptide** biosynthesis (GSH).
3- Synthesis of **non-protein nitrogenous (NPN)** compounds (creatine, urea, ammonia and uric acid).
4- Deamination & Transamination to synthesized a **new amino acid** or glucose or ketone bodies or **produce energy in starvation**.
Sources & fates of amino acids:

- Protein turnover: (results from simultaneous synthesis & breakdown of proteins molecules)
  - Total amount of protein in body of healthy adult is constant (due to rate of protein synthesis is equal to the rate of its breakdown).
Metabolism OF AMINO ACIDS:

1. Removal of amonia by:
   - Deamination
     - Oxidative deamination
       1) glutamate dehydrogenase in mitochondria
       2) amino acid oxidase in peroxisomes
     - Direct deamination (nonoxidative)
       1) dea. by dehydration (-H₂O)
       2) dea. by desulphuration (-H₂S)
   - Transamination (GPT & GOT)
   - and transdeamination.

2. Fate of carbon-skeletons of amino acids

3. Metabolism of ammonia
Deamination of Amino Acids

a) **Oxidative Deamination:**

1) Glutamate dehydrogenase, mitochondrial, potent, major deaminase

![Diagram of glutamate dehydrogenase reaction]

- **Reaction:**
  - **Input:** Glutamate + NAD (or NADP) + H₂O
  - **Output:** α-ketoglutarate + NH₃ + NADH + H⁺ (or NADPH + H⁺)

- **Regulation:**
  - Allosterically stimulated by ADP
  - Inhibited by ATP, GTP, and NADH

Thus, high ADP (low caloric intake) increases protein degradation, and high ATP (well fed-state) decreases deamination of amino acids and increases protein synthesis.
2) Amino Acid Oxidases:

The **minor** pathway for deamination of amino acids. They are found **in peroxisomes** of liver and kidney. **L**-amino acid oxidases utilize **FMN** while **D**-a.a. oxidases utilize **FAD**.
• **D-amino acid oxidases** are highly active than **L-amino acid oxidases** especially in kidney and liver **due to:**
  
  the function of D-amino acid oxidases is the rapid and irreversible breakdown of D-amino acids **since:**

• **D-amino acids** are potent inhibitors to **L-amino acids oxidases**
b) Non-oxidative deamination: (Direct Deamination)

1) Deamination by dehydration:
   Serine & Threonine
2) Deamination by desulfhydration (cysteine)
Transamination:

Aminotransferases are active both in cytoplasm and mitochondria e.g.:
1. Aspartate aminotransferase (AST), Glutamate oxaloacetate transaminase (GOT),
2. Alanine aminotransferase (ALT), Glutamate pyruvate transaminase, (GPT)

In all transamination reactions, α-ketoglutarate (α –KG) acts as amino group acceptor.
Most, but not all amino acids undergo transamination reaction with few exceptions (lysine, threonine and imino acids)
The role of PLP as Co-aminotransferase:
PLP binds to the enzyme via schiff’s base & ionic salt bridge & helps in transfer of amino group between amino acid and keto acid (KG):
It is an **exchange of amino nitrogen** between the molecules without a net loss.

**This metabolically important because:**

1) There is **no mechanism for storage** of a protein or amino acids.

2) In case of **low energy (caloric shortage)**, the organism depends on **oxidation of the ketoacids** derived from transamination of amino acids.

3) It is important for formation of the **non-essential amino acids**
Transdeamination:

Amino acid → Aminotransferase → α-ketoacid → Glutamate dehydrogenase → Transamination → Deamination with Glu.D.H. → Funnel → NH₃

Due to L-amino acid oxidases, but not glutamate dehydrogenase, can sluggish (decrease) the rate of deamination of the amino acids.

So... the most important and rapid way to deamination of amino acids is first transamination with α-ketoglutarate followed by deamination of glutamate.

Therefore glutamate through transdeamination serves to a funnel ammonia from all amino acids.
THE FATE OF CARBON-SKELETONS OF AMINO ACIDS

a) Simple degradation:
(amino acid → Common metabolic intermediate)
- Alanine → Pyruvate
- Glutamate → α-ketoglutarate
- Aspartate → Oxaloacetate

b) Complex degradation:
(amino acid --- Keto acid ----- complex pathway ---- Common metabolic intermediate)
Amino acids whose ketoacids are metabolized via more complex pathway e.g. Tyrosine, Lysine, Tryptophan

c) Conversion of one amino acid into another amino acid before degradation:
Phenylalanine is converted to tyrosine prior to its further degradation.
The common metabolic intermediates that arised from the degradations of amino acids are: acetyl CoA, pyruvate, one of the krebs cycle intermediates (α-ketoglutarate, succinyl CoA, fumarate& oxaloacetate).
Metabolism of the Common Intermediates

1. **Oxidation**: all amino acids can be oxidized in TCA cycle with energy production.

2. **Fatty acids synthesis**: some amino acids provide acetyl CoA e.g. leucine and lysine (ketogenic amino acids).

3. **Gluconeogenesis**: ketoacids derived from amino acids are used for synthesis of glucose (is important in starvation).

<table>
<thead>
<tr>
<th>Glucogenic</th>
<th>Ketogenic</th>
<th>Glucogenic &amp; Ketogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala, Ser, Gly, Cys, Arg, His, Pro, Glu, Gln, Val, Met, Asp, Asn.</td>
<td>Leu, Lys</td>
<td>Phe, Tyr, Trp, Ile, Thr</td>
</tr>
</tbody>
</table>
METABOLISM OF AMMONIA

Ammonia is formed in body from:

a) From amino acids: 1. Transdeamination in liver.
   2. Amino acid oxidases and amino acid deaminases in liver and kidney.

b) Deamination of physiological amines: by monoamine oxidase (histamine, adrenaline, dopamine and serotonin).

c) Deamination of purine nucleotides: especially adenine nucleotides

\[ \text{AMP} \xrightarrow{\text{deaminase}} \text{IMP} + \text{NH}_3 \]

d) Pyrimidine catabolism.

e) From bacterial action in the intestine on dietary protein & on urea in the gut.

\[ \text{NH}_3 \text{ is also produced by glutaminase on glutamine.} \]
Metabolic Disposal of Ammonia

Ammonia is toxic to CNS, it is fixed into nontoxic metabolite for reuse or excretion according to the body needs:

a) Formation of Glutamate:
   \[
   \alpha-KG + NH_3 \xrightarrow{GDH} \text{Glutamate} \xrightarrow{T.A.} \alpha\text{-Amino acid}
   \]

b) Glutamine Formation: Muscle, brain

Glutamine is storehouse of ammonia & transporter form of ammonia.

In brain, glutamine is the major mechanism for removal of ammonia while in liver is urea formation.

Circulating glutamine is removed by kidney, liver and intestine where it is deamidated by glutaminase.

c) Urea formation
This reaction is important to **kidney** due to kidney excretes NH$_4^+$ ion to keep extracellular Na$^+$ ion in body and to maintain the acid-base balance.
c) Urea Formation

- Urea is the principal end-product of protein metabolism in humans.
- It is important route for detoxication of NH₃.
- It is operated in liver, released into blood and cleared by kidney.
- Urea is highly soluble, nontoxic and has a high nitrogen content (46%), so ...it represents about 80-90% of the nitrogen excreted in urine per day in man.
- Biosynthesis of urea in man is an energy-requiring process.
- It takes place partially in mitochondria and partially in cytoplasm.
The Urea Cycle

(The Ornithine Cycle, Kreb's Henseleit Cycle):

1. Carbon dioxide provides the carbon atom of urea.
2. Free ammonia provides one of the nitrogen atoms of urea.
3. The enzyme has an absolute requirement for N-acetylglutamate, which acts as an allosteric activator.
4. Citrulline is transported out of the mitochondrion.
5. The amino group of aspartate provides one of the nitrogen atoms of urea.
6. Ornithine is regenerated and transported into the mitochondrion.
7. Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.
The Urea Cycle.

Metabolic Integration of Nitrogen Metabolism. The urea cycle, the citric acid cycle, and the transamination of oxaloacetate are linked by fumarate and aspartate.
Metabolic Significant Aspects of Urea Cycle

A) **Energy Cost**: Energy cost of the cycle is only one ATP.

B) **urea cycle is related to TCA cycle**:
   1. CO₂
   2. *Aspartate arises via transamination of oxaloacetate with glutamate*. Thus, depletion of oxaloacetate will decrease urea formation (as in malonate poisoning).
   3. *Fumarate* enters TCA cycle

C) **Sources of Nitrogen in urea**: free NH₃ and aspartate.

N.B. *glutamate* is the immediate source of both NH₃ (via oxidative deamination by Glu. Dehyd.) and *aspartate* nitrogen (through transamination of oxaloacetate by AST).
Importance of Urea Cycle

1. Formation of arginine (in organisms synthesizing arginine) & formation of urea (in ureotelic organisms, man) due to presence of arginase.

2. Liver shows much higher activity of arginase than brain or kidney for formation of urea while in brain or kidney is the synthesis of arginine.

Regulation of Urea Cycle

1) **Activity of individual enzymes:**

THE RATE LIMITING STEPS

a) carbamoyl phosphate synthase-1

b) Ornithine transcarbamylase.

c) Arginase.

- **N-acetylglutamate** is an activator for carbamoyl phosphate synthase-1.
  It enhances its **affinity** for ATP.
  It is **synthesized** from acetyl CoA and glutamate.
  Its hepatic concentration increases after intake of a **protein diet**, leading to an increased rate of urea synthesis.

- Activity of ornithine transcarbamylase is limited by the concentration of its **co-substrate** "ornithine".
2) Regulation of the flux through the cycle:

a) Flux of ammonia:
   1. by amino acids release from muscle (alanine, glutamine),
   2. metabolism of glutamine in the intestine
   3. amino acids degradation in the liver.

b) Availability of ornithine.

c) Availability of aspartate:
   since aspartate is required in equimolar amounts with ammonia, this is satisfied by of transdeamination.

3) Change in the level of Enzymes:

- Arginase & other urea-forming enzymes are adaptive enzymes thus
- a protein-rich diet will increase their biosynthesis rate & the opposite is true for low protein diet.
- However, in starvation, where the body is forced to use its own tissue protein as fuel, there is an increase in urea-forming enzymes.
• Human body is **unable to synthesize** the **methyl group** and obtain it from **diet**.
• The first: **met = S-adenosyl methionine** (methyl donor = CH₃) **involved** in **transmethylation reaction**
• The second: **tetrahydrofolic acid** (FH₄ or THF) which is a carrier of active one-carbon units (-CH₃, -CH₂, -CHO, -CHNH, -CH).

![Diagram of One-Carbon Fragment Metabolism](image-url)
The one-carbon group carried by THF is attached to its N⁵ or N¹⁰ or to both.

<table>
<thead>
<tr>
<th>Group</th>
<th>Position on THF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl:</td>
<td>N⁵</td>
</tr>
<tr>
<td>-CH₃</td>
<td></td>
</tr>
<tr>
<td>Methylene</td>
<td>N⁵, N¹⁰</td>
</tr>
<tr>
<td>-CH₂</td>
<td></td>
</tr>
<tr>
<td>Formyl</td>
<td>N⁵ or N¹⁰</td>
</tr>
<tr>
<td>-CHO</td>
<td></td>
</tr>
<tr>
<td>Formimino</td>
<td>N⁵</td>
</tr>
<tr>
<td>-CHNH</td>
<td></td>
</tr>
<tr>
<td>Methenyl</td>
<td>N⁵, N¹⁰</td>
</tr>
<tr>
<td>-CH</td>
<td></td>
</tr>
</tbody>
</table>
These one-carbon units are **interconvertible** to each other.

The primary **sources of one-carbon units** are serine, glycine, histidine, **tryptophan** & betaine.

and their **acceptors** for biosynthesis a variety of biomolecules are **Phosphatidylethanolamine**, **Guanidoacetic acid**, nor-**Epinephrine**, *Thymine*, **Purine-C8** & **Purine-C2** & homocysteine.
1. **Metabolism of Glycine**: nonessential, glucogenic.

**Biosynthesis of glycine:**

1. Serine $\rightarrow$ Hydroxymethyl transferase $\rightarrow$ Glycine synthase complex.

2. Glycine $\rightarrow$ Serine $\rightarrow$ Glycine synthase complex.

\[
\text{CO}_2 + \text{NH}_3 + N^5, N^{10}\text{CH}_2\text{THF} \rightarrow \text{Glycine} + \text{THF}
\]

\[
\text{Glycine synthase complex.}
\]

\[
\text{NADH} + \text{H}^+ \rightarrow \text{NAD}^+
\]

\[
\text{PLP}
\]

\[
\text{NADH} + \text{H}^+ \rightarrow \text{NAD}^+
\]

\[
\text{PLP}
\]
Degradative pathway: Hyperoxaluria

1. Reaction 2.

3. (CH₃)₃-N-CH₂ COO⁻ + Homocysteine → Met + (CH₃)₂-N -CH₂ COO⁻

Dimethylglycine

Betaine

\[ \text{HS-CH₂-CH₂-CH-COOH (Homocysteine)} \]

\[ \text{CH₃-S-CH₂CH₂-CH-COOH (methionine)} \]

Amino acid oxidase

\[ \text{H₂NCH₂COO⁻} \]

Glycine

\[ \text{CHO} + \text{NH₃} \]

COOH

\[ \text{COOH} \]

\[ \text{HCOOH} \]

Oxalate
Special Functions of Glycine:

- a-Protein, Hormones & enzymes.
- b-Heme
- c-Purines (C₄,C₅,N₇)
- d-Creatine
- e-Glutathione

f- Conjugating reactions:
- Glycine + Cholic acid → glycocholate.
- Glycine + Benzoic acid → Hippuric acid

1. Formation of Glutathione (GSH)

\[
\text{Glutamate} + \text{Cysteine} \xrightarrow{\gamma-\text{Glu} - \text{Cys synthase}} \gamma - \text{glutamyl Cysteine} + \text{Glycine} \\
\xrightarrow{\text{ATP} \rightarrow \text{ADP} + \text{Pi}} \gamma - \text{glutamyl cysteinyl glycine} (\text{GSH}) \xrightarrow{\text{ATP} \rightarrow \text{ADP} + \text{Pi}} \text{GSH synthase}
\]
2. Formation of creatine (Methyl guanidoacetate)
- Creatine is the storage form of high energy phosphate in muscle.
- Creatinine is excreted in urine & increases on kidney failure due to its filtration is decreased. Its level is constant per 24 hrs & is proportional to muscle mass in human.
2. **Metabolism of Serine**: nonessential & glucogenic

- It is synthesized from glycine or
- intermediate of glycolysis,
- all enzymes are activated by testosterone in liver, kidney & prostate.

\[ \text{3-phosphoglycerate} \xrightarrow{\text{Dehydrogenase}} \text{NAD} \xrightarrow{\text{NADH}+\text{H}^+} \text{3-phosphopyruvate} \]

\[ \text{3-phosphopyruvate} \xrightarrow{\alpha \text{KG}} \text{Glu} \]

\[ \text{Glu} \xrightarrow{\text{PLP}} \text{α KG} \]

\[ \text{α KG} \xrightarrow{\text{TA}} \text{3-phosphoserine} \]

\[ \text{3-phosphoserine} \xrightarrow{\text{Phosphatase}} \text{HO CH}_2 - \text{CH} - \text{COOH} \]

\[ \text{HO CH}_2 - \text{CH} - \text{COOH} \xrightarrow{\text{Pi} \xrightarrow{\text{H}_2\text{O}}} \text{Serine} \]
Degradiative Pathways of Serine:

1. Serine $\rightleftharpoons$ Glycine $\rightarrow$ CO$_2$+NH$_3$ (major)

2. Serine $\xrightarrow{\text{Ser. dehydratase}}$ Pyruvate + NH$_3$

   - PLP
   - Alanine $\rightarrow$ CO$_2$ + H$_2$O
   - Glucose

   - T.A.
   - TCA

Serine is important in synthesis of:

- a. Phosphoprotein
- b. Purines & pyrimidine
- c. Sphingosine
- d. Choline
- e. Cysteine
3. Metabolism of Sulfur-Containing amino acids
(Methionine, cysteine & Cystine):

a) Metabolism of methionine: (essential)

2 principal metabolic pathways:
Transmethylation and transsulfuration

Transmethylation
In transmethylation there are:

**Methyl acceptors**

1. Guanidoacetic acid
2. Norepinephrine
3. Ethanolamine
4. Uracil

**Methyl Compounds**

- Creatine
- Epinephrine
- Choline
- Thymine

SAM

SAH

(S-Adenosyl Homocysteine)
Homocystinuria
Lack of Cystathionine synthase

C-skeleton of cysteine
From serine & S from methionine

Transmethylation
Pi + PPI
S-adenosylmethionine
SAM synthase
ATP
SAM
S-adenosyl Homocysteine
Me-acceptor
Methyltransferase
Me-product

Heterocysteine
COOH
H2N-CH
CH2
CH2
SH
+ N5CH3H4FA
B12
Methyltransferase
adenosine
H2O

(Degradative pathway) or Transsulfuration

Cystathionase
H2O
Cystathionine

Cysteine
Homoserine

NH3
deaminase
PLP
NAD+
α-ketobutyrate
CoAS
CO2
propionyl CoA
Succinyl CoA.
b) **Metabolism of Cysteine & Cystine:**

- They are interconvertable & not essential.
- Can be synthesized from Met & Ser.
Degradative pathway of cysteine:

**Transamination**
- SH
- CH₂
- H₂NCH
- COOH
- Cysteine
- α-KG
- GLu
- TA
- PLP

**Oxidative pathway**
- Cys-dioxygenase
  - Fe⁺⁺, O₂
  - NADPH, NADP
- SO₂H
- CH₂
- CHNH₂
- COOH
- Cysteine-sulfinic acid
- Cys-sulfinate
- α KG, PLP
- GLu
- TA
- NH₃
- SO₃⁻⁻→SO₄⁻⁻
- B₆
- H₂S
- H₂O
- PAPS
- ATP

**Non oxid. pathway**
- 3-mercapto pyruvate
- Trans-sulfurase
- GSH
- MO²⁺, cyt b₅
- sulfite oxidase
- SO₄⁻⁻→SO₃⁻⁻→SO₄⁻⁻
- ATP
- PAPS (active SO₄)
Biochemical functions of cysteine

1- PAPS Formation: (3'-phosphoadenosine,5'-phosphosulphate)active sulphate used in formation of sulfate esters of steroids, alcohol, phenol, some lipids, proteins and mucopolysaccharides

2- Sulfur of COASH, GSH, vasopressin, insulin

3- Detoxication reaction of bromo, chloro, iodobenzene, naphthalene and anthracene & of phenol, cresol, indol and skatol that is formed by the action of intestinal bacteria on some amino acids in large intestine with formation of ethereal sulfates which is water soluble and rapidly removed by the kidney

4- Taurine Formation (with bile acids form taurocholate)
Polyamines (Spermidine & Spermine):

1. Spermine & spermidine are growth factors, so they are important in cell proliferation and growth.

2. They are important in stabilization of cells and subcellular organelles membranes.

3. They have multiple + Ve charges and associate with polyanions such as DNA, RNAs and have been involved in stimulation of RNA and DNA biosynthesis as well as their stabilization.

4. They exert diverse effects on protein synthesis and act as inhibitors of protein kinases.
Biosynthesis:

Met. → SAM → PLP → CO₂ → Ornithine → Decarboxylase → CO₂ → Decarboxylated SAM → Methylthioadenosine → Spermidine Synthase → Spermine Synthase → Spermine → Spermidine → 1,3 Diaminopropane → 1,4 Diaminobutane → Arginine
Catabolism of Polyamine

Spermine $\xrightarrow{\text{Polyamine oxidase}}$ Spermidine

$\text{O}_2$ $\xrightarrow{\text{Polyamine oxidase}}$ B-aminopropionaldehyde

$\text{CO}_2 + \text{NH}_3$ $\xrightarrow{\text{Putrescine}}$ $\text{H}_2\text{O}_2$

$\text{H}_2\text{O}_2$
4. Aromatic amino acids

a) Metabolism of Phenylalanine (glucogenic & ketogenic)

Phenylalanine

\[ \text{NH}_2 \text{CH}_2\text{CH COOH} \]

\[ \text{O}_2 \text{Phenylalanine hydroxylase} \Rightarrow \text{H}_2\text{O} \]

\[ \text{H}_4 \text{biopterine} \Rightarrow \text{H}_2 \text{biopterine} \]

\[ \text{NADP}^+ \Rightarrow \text{NADPH(H}^+) \]

Tyrosine

\[ \text{NH}_2 \text{CH}_2\text{CH COOH} \]

\[ \alpha \text{KG} \text{PLP Glu} \]

\[ \text{TA} \]

P-Hydroxyphenylpyruvate (PHPP)

\[ \text{OH} \]

Homogentisate

\[ \text{OH} \text{Homogentisate Oxidase} \Rightarrow \text{Fe}^{2+} \text{O}_2 \]

\[ \text{O} \text{Maleylacetoacetate isomerase} \Rightarrow \text{GSH} \]

\[ \text{C} \text{CH}_2\text{COOH} \text{GSH} \]

\[ \text{H}_2\text{O} \text{Hydrolase} \Rightarrow \text{Fumarate + Acetoacetate} . \]

\[ \text{O} \text{GSH} \]

\[ \text{Fumaryl acetoacetate} \]

\[ \text{H}_2\text{O} \]

\[ \text{Fumarate + Acetoacetate} . \]

\[ \text{glucose} \]

\[ \text{Ketone body} \]

\[ \text{P-Hydroxyphenylpyruvate (PHPP)} \]
b) Tyrosine is a precursor of:

1. DOPA (3,4 dihydroxy phenylalanine)
2. Thyroid hormones:

Thyroxine Formation:

3-Monoiodotyrosine (MIT)

3,5-Diiodotyrosine (DIT)

3,5,3'-Triiodothyronine (T₃)

3,5,3',5'-Tetraiodothyronine (T₄)

3,3',5'-Triiodothyronine (reverse T₃)
Thyroglobulin (Tgb)

- It is the precursor of $T_3$ and $T_4$
- It is large, iodinated, glycosylated protein.
- It contains 115 tyrosine residues each of which is a potential site of iodination.
- 70% iodide in Tgb exists in the inactive forms MIT&DIT WHILE
- 30% is in $T_3$ & $T_4$
- About 50 μg thyroid is secreted each day.
Biosynthesis of Thyroid hormones

Includes the following steps:

1. **Concentration of iodide:** the uptake of I by the thyroid gland is an energy dependent process & is linked to active Na pump.

2. **Oxidation of iodide:** the thyroid is the only tissue that can oxidize I to a higher valence state.

3. **Iodination of tyrosine:** oxidized I reacts with tyrosine residues in thyroglobulin form MIT & DIT.

4. **Coupling of iodotyrosyls:** The coupling of two DIT $\rightarrow$ T4 or of MIT & DIT $\rightarrow$ T3.
c) **Tryptophan** *(essential, glucogenic & ketogenic)*

I] **3-hydroxyanthranilic acid pathway:**

- Trp pyrrolase
  - Inc. by Cortico. & tryptophan
  - Dec. by Niacin, NAD & NADP

![Chemical pathway diagram](image-url)
**II] Serotonin Pathway:**

* Neurotransmitter

* Found in mast cells & platelets.

* Vasoconstrictor for B.V. & bronchioles

* Transmitter in GIT to release the peptide hormones.
Melatonin formation pathway

- It is the hormone of **pineal body** in brain of man. Formed by the acetylation and methylation of serotonin.
- It has effects on **hypothalamic-pituitary** system. It **blocks** the action of MSH & ACTH.
- It is important in regulation of **gonad & adrenal functions**.
- It has a **circadian rhythm** due to its formation occurs only **in dark**, due to high activity of **N-acetyl transferase enzyme** so it is a **biological clock**.
- It keeps the **integrity of cells** during aging due to it has an antioxidant property.
- It enhances the body defense against infection in AIDS patients by increasing the number of immune cells.
- It reduces the risk of cancer & heart diseases.
IV] Indol, skatol and indicant pathway:

- Indol & skatol contributes to unpleasant odour of feces.
- Skatoxyl and indoxyl are absorbed from **large intestine**
- and **conjugated** with sulfate in the **liver**
- and **excreted in urine** as indican (K indoxyl sulfate).

Bacteria in colon

- Tryptophan → indol acetic acid → Skatol
- indoxyl → indol → Skatoxyl

(indican)

\[
\text{Indoxyl} + \text{O}_2 \rightarrow \text{Indol} + \text{CO}_2
\]

\[
\text{Skatoxyl} + \text{O}_2 \rightarrow \text{Skatol} + \text{CO}_2
\]

\[
\text{K indoxyl sulfate}
\]
Aromatic Amino Acids

Phenylalanine → Tyrosine

Tryptophane

fumarate

Acetoacetate

Dopa & Dopamine

Melanine

Skatol & Indol

Melatonin

Nor epinephrin & epinephrine

Thyroxin

Anthranilic

Serotonin

glucose

ketone


Alanine

Nicotinamide

Acetoacetyl CoA
5. **Basic Amino Acids:**
   1) **Histidine (glucogenic amino acid):**

   a) Together with B-alanine, it forms **carnosine** (B-alanyl histidine) and **anserine** (methyl carnosine):

   1. They are **buffer the pH of anerobically contracting skeletal muscle**
   2. They **activate myosin ATP-ase**
   3. They **chelate copper and enhance Cu\(^{2+}\) uptake.**

   b) Histidine is a source of one-carbon atom.

   c) Histidine is a chemical messenger that mediates **allergic and inflammatory reactions**, **gastric acid secretion** and **neurotransmission in the brain**.
(2) **Arginine**: (nonessential & glucogenic amino acid):

It participates in formation of:

a) Creatine

b) Polyamines

C) Nitric oxide NO (Free radical gas).

\[
\text{L-Arginine} \rightarrow \text{NO synthase} \rightarrow \text{NADP}^+ \rightarrow \text{L-Citrulline}
\]

\[
\text{NADPH(H+)} \rightarrow \text{O}_2 \rightarrow \text{NO} \rightarrow \text{neurotransmitter in brain}
\]

relaxes smooth muscle (vasodilation)

prevents platelet aggregation

possesses tumoricidal and bactericidal action in macrophages.
3) **Lysine**: (essential, ketogenic)
   it is involved in the formation of histone, hydroxylysine & carnitine:

![Chemical structure diagram of Lysine, Trimethyl lysine, and related metabolites](image)
6. **Acidic Amino Acids:**

1. **Glutamic acid**: (nonessential & glucogenic amino acid).

   It participates in formation of:

1. GSH.

2. Glutamine: as storage and transporter form of ammonia.

3. GABA (δ-aminobutyric acid) neurotransmitter in brain.
2. **Aspartic acid**: Acidic, non essential & glucogenic

1. Arginosuccinate in urea cycle.
2. Alanine by decarboxylation.
3. Oxalate & glucose by T.A.

---

**Amino acids as precursors of neurotransmitters**

1. Arginine ------------ NO
2. Tryptophan--------- Serotonin
3. Histidine---------- Histamine
4. Phenyl alanine----- dopa, dopamine, NE&E
5. Glutamic acid------- GABA