Amino acid Metabolism

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Surat
Fates of carbon skeleton of amino acid

Glucose → Phosphoenol-pyruvate → Pyruvate → Acetyl CoA

Alanine, Cysteine, Glycine, Serine, Threonine, Tryptophan → Isoleucine, Leucine, Tryptophan

Leucine, Lysine, Phenylalanine, Tryptophan, Tyrosine

Asparagine, Aspartate, Phenylalanine, Tyrosine

Isoleucine, Methionine, Threonine, Valine

Oxaloacetate → Fumarate → Succinyl CoA

Citrate → α-Ketoglutarate

Arginine, Glutamate, Glutamine, Histidine, Proline

Fatty Acid
Overview of Phenylalanine & Tyrosine Metabolism

Phenylalanine → Phenylalanine hydroxylase → Tyrosine → Monoiodo Tyrosine → Thyroid Hormone

Dopamine ← Dopamine

Dopa ← Tyrosinase

Tyrosine ← Tyrosinase

4-hydroxyphenylpyruvate ← Homogentisic acid

Homogentisic acid oxidase

Maleylacetoacetate ← Fumarylacetoacetate

Fumarate + Acetoacetate

Phenylpyruvate ← Phenylpyruvate

Norepinephrine ← Melanine

Epinephrine

MAO COMT

Vanillylmandelic acid
Phenylalanine → Phenylpyruvic acid

Phenylketonuria block

Phenylalanine hydroxylase

Tyrosine

Albinism block

3,4-Dihydroxyphenylalanine (DOPA)

Melanin pigments

CO₂ + H₂O

Citric acid cycle

Acetoacetic acid

Fumaric acid

Fumarylacetoacetic acid

Maleylacetoacetic acid

Tyrosinemia block

Tyrosine transaminase

p-Hydroxyphenylpyruvic acid

Homogentisic acid oxidase

Homogentisic acid (2,5-dihydroxyphenylacetic acid)

Alkaptonuria block
Alternate pathways in PKU
Alkaptonuria

- Inherited disorder of the Tyrosine metabolism
- Absence of Homogentisate oxidase.

- Homogentisic acid is accumulated
- Excreted in the urine
- Turns black (Benzoquinone Acetate) on exposure to air

Clinical Features

- In children:
  - Urine in diaper = Black Stain
- In adults:
  - Connective tissue Pigmentation (Ochronosis)
  - Darkening of the Ear
  - Dark spots on the sclera and cornea
Accumulation of oxidized homogentisic acid in connective tissue

Arthritis of the Spine

Urine turns a black color upon exposure to air

Aortic valve Stenosis
Diagnosis

- Benedict Test
  - Urine Sample = Homogentisic Acid
  - Positive test
- Imaginary Study
- Chromatography
Phenylalanine to Tyrosine

Phenylalanine hydroxylase

Phenylalanine

Tyrosine

$\text{H}_4\text{biopterin}$

$\text{H}_2\text{biopterin}$

Dihydropteridine reductase

$\text{NAD}^+$

$\text{NADH} + \text{H}^+$
Phenylketonuria = Biochemical Alteration

• No Dopamine
  – Extrapyramidal manifestation (Parkinsonism)
  – Seizure
  – Hypotonia
  – Tremor
• No Epinephrine
• No Norepinephrine
• No Melanin
  – Light colour skin
  – Eye abnormality = Hypopigmentation
• No Thyroid hormone
  – Physical & Mental Growth retardation
Phenylketonuria = Biochemical Alteration

• Accumulation of Phenylalanine (Large Neutral)
  – Restrict entry of some other Large neutral AA
  – Decrease synthesis of Other Neurotransmitter
  – Decrease Interactuall activity

• Accumulation of Phenylacetate
  – “Musty Odour” Urine & Sweat
Phenylketonuria Diagnosis

- Ferric Chloride Test
- Guthrie test = Screening Neonate
- Tandem Mass spectroscopy
- Genetic Study
Guthrie Test
Screening by Bacterial Inhibition

Grown E.Coli on Media With Phenylalanine

E.Coli on Media with Beta 2thienylalanine (Inhibit Bacteria Growth)

If Patient sample has Excess Phenylalanin, it counter inhibition and E.Coli will grow
Albinism = Deficiency of Tyrosinase
Symptoms of Albinism

- lack of melanin in skin, hair, eyes
- Increased sensitivity to sunlight
Tryptophane Metabolism

Tryptophan → N-formyl kynurenine → Formyl THFA

5-OH-tryptophan → Kynurenine

Serotonin

Pyridoxal Phosphate → Kynureninase

3-hydroxy kynurenine → 3-OH anthranilic acid

MAO

Melatonin

5-HIAA

Niacin → NAD⁺
Carcinoid Syndrome

• Carcinoid Tumour = Tumour of Endocrine gland

• Paraneoplastic Syndrome
  – This Malignant cell produce “Hormone”

• In Carcinoid Tumor = Paraneoplastic Syndrome
  = Carcinoid Syndrome

• Increase Production of Serotonin from Tryptophan
• Decrease Production of Niacin
• Patient Suffer from Pellagra
Monoamino Oxidase Inhibitor

- Decrease Break down of Serotonin
- Increase Level of Serotonin
- Clinical Useful in
  - Depression
  - Schizophrenia
- As well As Increase level of
  - Epinepherin
  - Norepinepherin
  - Dopamine
Methionine Metabolism

- Methionine
- S-adenosylmethionine
- \( \chi \) (e.g. DNA, protein, lipids)
- 5-Me-TH\(_4\)-Folate
- TH\(_4\)-Folate
- Methyl Transferase
- FOLATE CYCLE
- Methionine synthase
- B12
- Homocysteine
- S-adenosylhomocysteine
- Cystathionine
- \( \beta \)-synthase
- B6
- Cysteine
- Glutamate-cysteine ligase
- Glutathione synthase
- Glutathione (GSH)
- ATP
- P\(_i\)+PP\(_i\)
- Adenosine
Folate Trap

- Vitamin B 12 deficiency
- Decrease Methionine synthase activity
- 5 – methyl- THF can not converted to THF
- No methyl group transfer
- No Methionine
- No SAM
  - DNA replication affected
  - Increase Homocysteine level
Hyperhomocysteinemia

Ectopia lentis = Dislocation of Eye lens
Hartnup Disease

Etiology
  Genetic Disorder
  Autosomal Recessive

Pathogenesis
Failure of Amino Acid (Non-Polar Amino acid )Transport
  In Intestine
  In Kidney
Decrease absorption of Tryptophan
Decrease Reabsorption of Tryptophan
Increase Loss of Tryptophan

Clinical Feature
  Pellagra
  Fanconi Syndrome

Etiology
  Congenital or Acquired
**Hartnup Disease**

**Etiology**
- Genetic Disorder
- Autosomal Recessive

**Pathogenesis**
- Failure of Amino Acid (Non-Polar Amino acid) Transport
  - In Intestine & Kidney
- Decrease absorption of Tryptophan
- Decrease Reabsorption of Tryptophan
- Increase Loss of Tryptophan

**Clinical Feature**
- Pellagra

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**Fanconi Syndrome**

**Etiology**
- Congenital or Acquired

**Pathogenesis**
- Inadequate absorption in Proximal Renal Tubules
- Reabsorption of Amino acid, Glucose, Uric acid, Phosphate, Bicarbonate

**Clinical Feature**
- Polyuria, Polydipsia & dehydration
- Hypophosphatemia
- Rickets.
- Osteomalacia (in adults)
- Growth failure
- Metabolic Acidosis
- Hypokalemia
- Hyperchloremia
Histidine \xrightarrow{\text{Decarboxylase}} \text{Histamine}
Creatine & Creatinine Synthesis

Arginine → Guanidoacetate
  ↓
  Glycine
  ↓
  Ornithine
  ↓
  SAM
  ↓
  SAH
  ↓
  Creatinine

(Kidney) ARGININE-GLYCINE TRANSAMIDINASE

(Liver) GUANIDOACETATE METHYLTRANSFERASE

ATP → ADP

NONENZYMATIC IN MUSCLE

Creatine Phosphate

$\text{HN} = \text{C} - \text{N} - \text{CH}_2 - \text{CH}_3$

$\text{HN} = \text{C} - \text{N} - \text{CH}_2 - \text{COO}^-$
Neurological Symptoms – Cerebral damage
Diarrhea, Vomiting, Weight Loss, Anorexia