AMINO ACID METABOLISM
Dynamics of Protein And Amino Acid Metabolism

Dietary Proteins $\rightarrow$ Digestion to Amino Acids $\rightarrow$ Transport in Blood to Cells

Protein Synthesis $\rightarrow$ Functional Proteins $\rightarrow$ Protein Degradation In Proteasomes Following Tagging With Ubiquitin

Amino Acids $\leftrightarrow$ Metabolites
Digestion of Proteins

Stomach: Pepsinogen $\rightarrow$ Pepsin (max. act. pH 2)

Small Intestine: Trypsinogen $\rightarrow$ Trypsin

Trypsin cleaves:
- Chymotrypsinogen to chymotrypsin
- Proelastase to elastase
- Procarboxyypeptidase to carboxyypeptidase

Aminopeptidases (from intestinal epithelia)
Intestinal Absorption

Amino Acids  Oligopeptides

Lumen

Transport Protein

Oligopeptides

Peptidases

Amino Acids

Blood
Incorporation of NH$_4^+$ Into Organic Compounds

1) NH$_4^+$ + HCO$_3^-$ + 2 ATP $\xrightarrow{\text{Carbamoyl Phosphate Synthase I (CPS-I)}}$ NH$_2$CO$_2$PO$_3^{-2}$ + 2 ADP + Carbamoyl Phosphate + P$_i$ + 2 H$^+$

2) NH$_4^+$ + $\text{O}_2\text{CCH}_2\text{CH}_2\text{CCO}_2^-$ $\xrightarrow{\text{Glutamate dehydrogenase}}$ $\text{NH}_3^+$ + $\text{O}_2\text{CCH}_2\text{CH}_2\text{CHCO}_2^-$

TCA Cycle

"\text{Carbamoyl Phosphate}"

mitochondria

\(\text{NADPH} + \text{H}^+\)
Incorporation of $\text{NH}_4^+$ Into Organic Compounds (Cont.)

3) $\text{NH}_3^+ + \text{O}_2\text{CCH}_2\text{CH}_2\text{CHCO}_2^- + \text{NH}_4^+ + 2 \text{ATP}$

Glutamate

Glutamine Synthase
$\text{Mg}^{++}$

Glutamine

$\text{H}_2\text{NCCCH}_2\text{CH}_2\text{CHCO}_2^-$

N of glutamine donated to other compounds in synthesis of purines, pyrimidines, and other amino acids
Biosynthesis of Amino Acids: Transaminations

\[ \text{Amino Acid}_1 + \alpha\text{-Keto Acid}_2 \rightleftharpoons \text{Amino Acid}_2 + \alpha\text{-Keto Acid}_1 \]

Glutamate

\[ \text{NH}_3^+ \quad \text{O}_2\text{CCH}_2\text{CH}_2\text{CHCO}_2^- \]

\[ \alpha\text{-Ketoglutarate} \]

Pyridoxal phosphate (PLP)-Dependent Aminotransferase

\[ \text{O} \quad \text{R}-\text{CCO}_2^- \]

\[ \text{NH}_2 \quad \text{R}-\text{CHCO}_2^- \]
Transaminations: Role of PLP
Blood levels of these aminotransferases, also called transaminases, are important indicators of liver disease.
Metabolic Classification of the Amino Acids

- Essential and Non-essential

- Glucogenic and Ketogenic
Non-Essential Amino Acids in Humans

- Not required in diet
- Can be formed from $\alpha$-keto acids by transamination and subsequent reactions

- Alanine
- Asparagine
- Aspartate
- Glutamate
- Glutamine
- Glycine
- Proline
- Serine
- Cysteine (from Met*)
- Tyrosine (from Phe*)

* Essential amino acids
Essential Amino Acids in Humans

- Required in diet
- Humans incapable of forming requisite carbon skeleton

- Arginine*
- Histidine*
- Isoleucine
- Leucine
- Valine
- Lysine
- Methionine
- Threonine
- Phenylalanine
- Tryptophan

* Essential in children, not in adults
Glucogenic Amino Acids

- Aspartate
- Asparagine
- Arginine
- Phenylalanine
- Tyrosine
- Isoleucine
- Methionine
- Valine
- Glutamine
- Glutamate
- Proline
- Histidine
- Alanine
- Serine
- Cysteine
- Glycine
- Threonine
- Tryptophan

Metabolized to $\alpha$-ketoglutarate, pyruvate, oxaloacetate, fumarate, or succinyl CoA

Phosphoenolpyruvate $\rightarrow$ Glucose
Ketogenic Amino Acids

- Metabolized to acetyl CoA or acetoacetyl CoA

Animals cannot convert acetyl CoA or acetoacetyl CoA to pyruvate

- Isoleucine
- Leucine *
- Lysine *
- Threonine

- Tryptophan
- Phenylalanine
- Tyrosine

* Leucine and lysine are only ketogenic
Amino Acids Formed From $\alpha$-Ketoglutarate

$\alpha$-Ketoglutarate $\rightarrow$ Transamination or Glutamate dehydrogenase

$\rightarrow$ Glutamate $\rightarrow$ Glutamine synthase

Glutamine $\rightarrow$ Glutamine synthase

Glutamine $\rightarrow$ Urea Cycle

Guanidino group $\rightarrow$ Arginine

Proline $\rightarrow$ Ornithine

4 Steps

5 Steps
GABA is an important inhibitory neurotransmitter in the brain. Drugs (e.g., benzodiazepines) that enhance the effects of GABA are useful in treating epilepsy.
Arginine Synthesis: The Urea Cycle

Glutamate + NH₃ → N-Acetylglutamate synthase

Activates

Carbamoyl phosphate

N-Acetylglutamate + Ornithine → Urea group

Ureido group

Citrulline

Ornithine transcarbamoylase (OTC) (mitochondria)

CPS-I

NH₄⁺ + HCO₃⁻ → NH₂CO₂PO₃⁻²

4 Steps
Formation of Serine

Glucose → Glycolysis → 3-Phosphoglycerate → 3-Phosphohydroxypyruvate

- Dehydrogenase: $\text{NAD}^+ \rightarrow \text{NADH} + \text{H}^+$
- Inhibits

Pyruvate → 3-Phosphoserine → Serine (Ser)

- Phosphatase

Glutamate → Transaminase: $\alpha$-Ketoglutarate

3-Phosphoserine → Serine (Ser)
Conversion of Serine to Glycine

Folate → Dihydrofolate reductase → Tetrahydrofolate (FH₄) → Serine hydroxymethyl transferase (PLP-dep.) → Glycine

Key intermediate in biosynthesis of purines and formation of thymine

Important in biosynthesis of heme, porphyrins, and purines
Sulfur-Containing Amino Acids

Methionine (Essential)

\[ \text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCO}_2^- \] + \( \text{NH}_3^+ \text{ FH}_4 \)

Methionine Synthase (Vit. B12-dep.)

\[ \text{HSCH}_2\text{CH}_2\text{CHCO}_2^- \] + \( \text{NH}_3^+ \text{ 5-Methyl FH}_4 \)

L-Homocysteine

Cystathionine \( \beta \)-synthase (PLP-dep.)

\[ \text{Cys} \text {CO}_2^- \]

Cystathionine lyase

\[ \text{NH}_3^+ \text{ 5-Methyl FH}_4 \]

Serine

\[ \text{CH}_3\text{CHCH}_2\text{CO}_2^- \]

\( \beta \)-Hydroxybutyrate

Cysteine (Non-essential)

\[ \text{SCH}_2\text{CH}_2\text{CHCO}_2^- \]

Cystathionine

\[ \text{CH}_2\text{CHCO}_2^- \]

OH

\[ \text{CH}_3\text{CHCH}_2\text{CO}_2^- \] + \( \text{HSCH}_2\text{CHCO}_2^- \)

\[ \text{NH}_3^+ \text{ FH}_4 \]

Cystathionine lyase
Homocysteinurie
- Rare; deficiency of cystathionine β-synthase
- Dislocated optical lenses
- Mental retardation
- Osteoporosis
- Cardiovascular disease → death

High blood levels of homocysteine associated with cardiovascular disease
- May be related to dietary folate deficiency
- Folate enhances conversion of homocysteine to methionine
Methionine Metabolism: Methyl Donation

\[
\text{CH}_3\text{SCH}_2\text{CH}_2\text{CHCO}_2^- + \text{NH}_3^+ \rightarrow \text{S-Adenosyl methionine synthase} \rightarrow \text{ATP} \rightarrow \text{S-Adenosyl methionine (SAM)}
\]

Decarboxylated SAM

\[
\text{NH}_2\text{CH}_2\text{CH}_2\text{N} + \text{NH}_3^+ \rightarrow \text{CO}_2 \rightarrow \text{S-Adenosyl homocysteine}
\]

Methyl-transferases

\[
\text{R-H} \rightarrow \text{R-CH}_3
\]
Creatine and Creatinine

\[
\begin{align*}
\text{Arginine} & \quad \text{Glycine} & \quad \text{Ornithine} \\
\text{Guanidoacetate} & \quad S\text{-Adenosyl-homocysteine} & \quad \text{ADP} \\
\text{SAM} & \quad \text{ATP} & \quad \text{Phosphocreatine}
\end{align*}
\]
Creatine:  
- Dietary supplement  
- Used to improve athletic performance

Creatinine:  
- Urinary excretion generally constant; proportional to muscle mass

Creatinine Clearance Test:  
- Compares the level of creatinine in urine (24 hrs.) with the creatinine level in the blood  
- Used to assess kidney function  
- Important determinant in dosing of several drugs in patients with impaired renal function
Histidine Metabolism: Histamine Formation

Histidine:  
-Synthesized in and released by mast cells  
-Mediator of allergic response: vasodilation, bronchoconstriction (H₁ receptors)  
  -H₁ blockers: Diphenhydramine (Benadryl), Loratidine (Claritin)  
-Stimulates secretion of gastric acid (H₂ receptors)  
  -H₂ blockers: Cimetidine (Tagamet); ranitidine (Zantac)
Phenylalanine and Tyrosine

Phenylalanine (Essential)

Tyrosine (Non-essential)

O₂

H₂O

Phenylalanine-4-Monooxygenase (Phenylalanine hydroxylase)

NH₃⁺

CH₂CHCO₂⁻

O₂

H₂O

Phenylalanine-4-Monooxygenase (Phenylalanine hydroxylase)

NH₃⁺

CH₂CHCO₂⁻

NADP⁺

NADPH + H⁺

Tetrahydrobiopterin (BH₄)

Dihydrobiopterin

H₂N

N

N

H

H₂N

O

CHCHCH₃

HO

OH
Normal Utilization of Phenylalanine

Phenylalanine

Protein (~25%)

Tyrosine (~75%)
Deficiency of Phe hydroxylase

Occurs in 1:20,000 live births in U.S.

Seizures, mental retardation, brain damage

Treatment: limit phenylalanine intake

Screening of all newborns mandated in all states
Catecholamine Biosynthesis

Tyrosine → Dihydroxyphenylalanine (DOPA) → Dopamine → Norepinephrine → Epinephrine (Adrenaline)

DOPA, dopamine, norepinephrine, and epinephrine are all neurotransmitters.
Tyrosine catabolism

Tyrosine

$\text{NH}_3^+$ Transamination $\text{HO}$

$\text{CH}_2\text{CHCO}_2^-$

$p$-Hydroxyphenylpyruvate

Homogentisate dioxygenase

$\text{O}_2$

Homogentisate

$\text{O}_2$

$\text{CO}_2$

Fumarate + acetoacetate

Deficient in alkaptonuria

Cleavage of aromatic ring

$p$-Hydroxyphenylpyruvate dioxygenase (ascorbate-dep.)
Melanin Formation

Tyrosine: \[ \text{HO-CH}_{2}-\text{CHCO}_{2}^{-} \]

Tyr hydroxylase: \[ \text{OH} \rightarrow \text{NH}_{3}^{+} \]

DOPA: \[ \text{HO-CH}_{2}-\text{CHCO}_{2}^{-} \]

Tyrosinase: \[ \text{DOPA} \rightarrow \text{Dopaquinone} \]

Melanin (Black polymer): \[ \text{O} \rightarrow \text{O} \]

Highly colored polymeric intermediates

Melanin formed in skin (melanocytes), eyes, and hair
In skin, protects against sunlight
Albinism: genetic deficiency of tyrosinase
Tryptophan Metabolism: Serotonin Formation

Tryptophan (Trp) is converted to 5-Hydroxytryptophan through the action of Trp hydroxylase, which requires oxygen ($\text{O}_2$) and an ammonia ($\text{NH}_3$) group. The decarboxylation of 5-Hydroxytryptophan yields 5-Hydroxytryptamine (5-HT), also known as Serotonin.

Indole ring
Serotonin

• Serotonin formed in:
  • Brain (neurotransmitter; regulation of sleep, mood, appetite)
  • Platelets (platelet aggregation, vasoconstriction)
  • Smooth muscle (contraction)
  • Gastrointestinal tract (enterochromaffin cells - major storage site)

• Drugs affecting serotonin actions used to treat:
  • Depression
    • Serotonin-selective reuptake inhibitors (SSRI)
  • Migraine
  • Schizophrenia
  • Obsessive-compulsive disorders
  • Chemotherapy-induced emesis

• Some hallucinogens (e.g., LSD) act as serotonin agonists
L-Tryptophan

- Food supplement promoted for serotonin effects
- L-Tryptophan disaster (1989):
  - Eosinophilia-myalgia syndrome (EMS)
    - Severe muscle and joint pain
    - Weakness
    - Swelling of the arms and legs
    - Fever
    - Skin rash
    - Eosinophilia
    - Many hundreds of cases; several deaths
    - Traced to impurities
Serotonin Metabolism: 5-HIAA

Carcinoid tumors:
- Malignant GI tumor type
- Excretion of large amounts of 5-HIAA

5-Hydroxyindole acetic acid (5-HIAA) (Urine)
Serotonin Metabolism: Melatonin

Melatonin:
- Formed principally in pineal gland
- Synthesis controlled by light, among other factors
- Induces skin lightening
- Suppresses ovarian function
- Possible use in sleep disorders
Tryptophan Metabolism: Biosynthesis of Nicotinic Acid

Several steps

Nicotinic acid (Niacin)

Nicotinamide adenine dinucleotide (NAD)