Conversion of Amino Acids to Specialized Products

First Lecture
- Dietary protein
- Body proteins ↔ Amino acids

Second lecture
- Urea → NH₃
- Acetyl CoA
- Fats, sterols
- Carbohydrate intermediates
- Oxygen (O₂) → CO₂, H₂O, energy

Third Lecture
- Coenzymes
- Neurotransmitters
- Phospholipids
- Porphyrins
- Purines
- Pyrimidines
- Other nitrogenous compounds
Nitrogen-containing Compounds

Amino Acids
Synthesis of neurotransmitters
## TYROSINE-DERIVED NEUROTRANSMITTERS

### Catecholamines

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Amino Acid</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (Adrenaline)</td>
<td>Tyrosine</td>
<td>adrenal medulla, some CNS cells</td>
</tr>
<tr>
<td>Norepinephrin (Noradrenaline)</td>
<td>Tyrosine</td>
<td>CNS, sympathetic nerves</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Tyrosine</td>
<td>CNS (Dopaminergic neurons)</td>
</tr>
</tbody>
</table>

* Secreted upon stress

* regulators of carbohydrates and lipid metabolism
Synthesis of Catecholamines

Tyrosine

Tyrosine hydroxylase

3,4-Dihydroxyphenylalanine (dopamine)

DOPA-decarboxylase

Dopamine

Ascorbate + O₂

Dehydroascorbate + H₂O

Tyrosine synthesis

Phenylalanine

Phenylalanine hydroxylase

Tyrosine

Tetrahydrobiopterin (BH₄)

Dihydrobiopterin

Dihydropteridine reductase

NAD⁺

H₂O

GTP

A deficiency in dihydrobiopterin reductase or any of the enzymes of BH₄ synthesis leads to hyperphenylalaninemia, and decreased synthesis of catecholamines and serotonin.
Degradation of Catecholamine

Step I: Oxidative deamination by Monoamine oxidase

Step II: O-methylation carried out by catechol-O-methyl transferase

MAO inhibitors and methamphetamine block catecholamine degradation, allowing their accumulation in the presynaptic neuron and subsequent leakage into circulation, providing an antidepressant action.
Tryptophan-Derived Neurotransmitters

Serotonin (5-hydroxytryptamine) is involved in regulating appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system.

Melatonin (N-acetyl-5-methoxytryptamine) is another neurotransmitter derived from tryptophan.
Tryptophan-Derived Neurotransmitters

**Serotonin (5-hydroxytryptamine)**

![Diagram of the serotonin biosynthesis pathway](Diagram)

- **Tryptophan** is the starting point.
- **Tryptophan Hydroxylase** catalyzes the hydroxylation of tryptophan to 5-hydroxytryptophan.
- **Aromatic L-amino acid decarboxylase** decarboxylates 5-hydroxytryptophan to serotonin.

Chemical structures and reactions in detail:

1. Tryptophan + Tetrahydrobiopterin + O₂ → 5-Hydroxytryptophan
2. 5-Hydroxytryptophan + Dihydrobiopterin + H₂O → Serotonin + CO₂

**Note:** The diagram illustrates the conversion pathway from tryptophan to serotonin.
After release from serotonergic neurons, most of the released serotonin is recaptured by an active reuptake mechanism.
Selective Serotonin reuptake inhibitors

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Serotonin is a neurotransmitter that passes messages between nerve cells that are involved in depression.
Melatonin is derived from serotonin within the pineal gland and the retina that contain N-acetyltransferase enzyme.

Melatonin

* Synthesis and secretion of melatonin increases during the dark period of the day and is maintained at a low level during daylight hours.

* Norepinephrine regulates melatonin secretion through interaction with β-adrenergic receptors.

* This leads to increased levels of cAMP, which in turn activate the N-acetyltransferase required for melatonin synthesis.

N-acetyl-5-methoxytryptamine
Creatine is used as a storage form of high energy phosphate.

The phosphate of ATP is transferred to creatine, generating creatine phosphate, through the action of creatine phosphokinase.

The reaction is reversible such that when energy demand is high (e.g. during muscle exertion) creatine phosphate donates its phosphate to ADP to yield ATP.

Both creatine and creatine phosphate are found in muscle, brain and blood.

Excreted by Kidneys
Guanidoacetate itself is formed in the kidney from the amino acids arginine and glycine.

Creatine is synthesized in the liver by methylation of guanidoacetate using SAM as the methyl donor.
Glutathione (abbreviated GSH) is a tripeptide composed of glutamate, cysteine and glycine.

Functions:
1) Glutathione serves as a reductant; it is an anti-oxidant.

2) It is involved in amino acid transport across cell membranes (the γ-glutamyl cycle);

3) It is a substrate for the peptido-leukotrienes;

4) serves as a cofactor for some enzymatic reactions and as an aid in the rearrangement of protein disulfide bonds.
Glutathione (GSH) is an antioxidant.

First, \( \gamma \)-glutamylcysteine is synthesized from L-glutamate and cysteine via the enzyme \( \gamma \)-glutamylcysteine synthetase.

Second, glycine is added to the C-terminal of \( \gamma \)-glutamylcysteine via the enzyme glutathione synthetase.
Polyamine Biosynthesis

Because the polyamines are highly cationic and tend to bind nucleic acids with high affinity, it is believed that the polyamines are important participants in DNA synthesis, or in the regulation of that process.

DNA replication

- elevated levels of mRNA for ornithine decarboxylase (ODC),
- first enzyme in the pathway to synthesis of the polyamines.
The key features of the pathway are that it involves putrescine, an ornithine catabolite, and S-adenosylmethionine (SAM) as a donor of 2 propylamine residues.

The first propylamine conjugation yields spermidine and addition of another to spermidine yields spermine.

The butylamino group of spermidine is used in a posttranslational modification reaction important to the process of translation. A specific lysine residue in the translational initiation factor eIF-4D is modified.
Nitric Oxide Synthesis

NO is an important messenger molecule involved in many physiological and pathological processes within the mammalian body.
Nitric Oxide Function

NO that are important for blood coagulation; it inhibits platelet aggregation.

Under physiological conditions, blood coagulation is prevented by the endothelium. This provides a physical barrier and secretes platelet inhibitory products, such as prostacycline (PGI2) and nitric oxide (NO).

NO limits platelet activation, adhesion and aggregation, and restricts recruitment of platelets to the initial platelet plug.

NO is also generated by cells of the immune system and as such is involved in non-specific host defense mechanisms and macrophage-mediated killing.

NO also inhibits the proliferation of tumor cells and microorganisms. Additional cellular responses to NO include induction of apoptosis (programmed cell death), DNA breakage and mutation.
**Histamine** is a local immune response and a neurotransmitter.

Histamine triggers the inflammatory response.

Histamine increases the permeability of the capillaries to white blood cells and other proteins, in order to allow them to engage foreign invaders in the infected tissues.
Melanin

L-Phenylalanine, L-tyrosine, and L-DOPA, are all are precursors to the biological pigment melanin. The enzyme tyrosinase catalyzes the oxidation of L-DOPA to the reactive intermediate, which reacts further, eventually leading to melanin oligomers.

It is a pigment that occurs in several tissues like eye, hair, and skin. Protect unerlying cells from sunlight. Synthesized from Tyrosine and Tyrosinase enzyme.
Incidence of inherited diseases of amino acid metabolism. [Note: Cystinuria is the most common genetic error of amino acid transport.]
# Six disorders of the urea cycle.

<table>
<thead>
<tr>
<th>Location</th>
<th>Abb.</th>
<th>Enzyme</th>
<th>Disorder</th>
<th>Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondria</td>
<td>NAGS</td>
<td>N-Acetylglutamate synthetase</td>
<td>N-Acetylglutamate synthetase deficiency</td>
<td>+Ammonia</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>CPS1</td>
<td>Carbamoyl phosphate synthetase I</td>
<td>Carbamoyl phosphate synthetase I deficiency</td>
<td>+Ammonia</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>OTC</td>
<td>Ornithine transcarbamylase</td>
<td>Ornithine transcarbamylase deficiency</td>
<td>+Ornithine, +Uracil, +Orotic acid</td>
</tr>
<tr>
<td>Cytosol</td>
<td>AS</td>
<td>Argininosuccinic acid synthetase</td>
<td>&quot;AS deficiency&quot; or citrullinemia</td>
<td>+Citrulline</td>
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<td>AL</td>
<td>Argininosuccinase acid lyase</td>
<td>&quot;AL deficiency&quot; or argininosuccinic aciduria (ASA)</td>
<td>+Citrulline, +Argininosuccinic acid</td>
</tr>
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<td>Cytosol</td>
<td>AG</td>
<td>Arginase</td>
<td>&quot;Arginase deficiency&quot; or argininemia</td>
<td>+Arginine</td>
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</table>
Cysteineurea

Cystinuria is a disorder of the proximal tubule’s reabsorption of filtered cystine and dibasic amino acids (lysine, ornithine, arginine).

The inability to reabsorb cystine leads to accumulation and subsequent precipitation of stones of cystine in the urinary tract.
Caused by a deficiency of the enzyme histidase.

Rare disease. However, in Japan, it is the single most prevalent inborn error of metabolism.
A **deficiency in phenylalanine hydroxylase** results in the disease phenylketonuria (PKU).

Deficiency of Dihydropteridine reductase

400 mutations in PAH gene are found
Phenylketonuria

A deficiency in dihydrobiopterin reductase or any of the enzymes of BH₄ synthesis leads to hyperphenylalaninemia, and decreased synthesis of catecholamines and serotonin.
Phenylketonuria

Characteristics of classic PKU:

- These metabolites give urine a characteristic musty (“mousey”) odor.
- Hypopigmentation
- CNS symptoms, Mental retardation, failure to walk or talk, seizures, hyperactivity, tremor, microcephaly, and failure to grow
Phenylbutyrate is a prodrug that is rapidly converted to phenylacetate, which combines with glutamine to form phenylacetylglutamine. The phenylacetylglutamine, containing two atoms of nitrogen, is excreted in the urine, thus assisting in clearance of nitrogenous waste.
Phenylketonuria

Treatment

Neonatal screening and diagnosis of PKU:
*Early diagnosis of phenylketonuria is important because the disease is treatable by dietary means.

*Because of the lack of neonatal symptoms, laboratory testing for elevated blood levels of phenylalanine is mandatory for detection.
Maple syrup urine disease

Catabolism of the branched-Chain amino acids

Essential aa

TRANSAMINATION
(Branched-chain $\alpha$-amino acid transferase)

$\alpha$-Ketoisocaproic acid $\alpha$-Ketoisovaleric acid $\alpha$-Keto-$\beta$-methylvaleric acid

Maple Syrup Urine disease

OXIDATIVE Decarboxylation
Branched-chain $\alpha$-keto acid dehydrogenase

Isovaleryl CoA Isobutyryl CoA $\alpha$-Methyl butyryl CoA

FAD-linked DEHYDROGENATION

Acetoacetate + Acetyl CoA
Propionyl CoA Acetyl CoA

Succinyl CoA
Maple syrup urine disease

\(\alpha\)-keto acids accumulate in the blood, causing a toxic effect that interferes with brain functions.

The disease is characterized by vomiting, dehydration, severe metabolic acidosis, and a characteristic maple syrup odor to the urine.
Albinism

Deficiency of tyrosinase → Melanine

Patient with aculocutaneous albinism showing white eyebrows and lashes

Vision defects
Increased risk of skin cancer
Homocysteinurea

Cause: Defect in Cystathione β-synthetase

Characterization: high plasma and urinary levels of homocysteine and methionine, and low levels of cysteine.

Symptoms: ectopia lentis (displacement of the lens of the eye), skeletal abnormalities, premature arterial disease, osteoporosis, and mental retardation.

Treatment: Restriction of methionine intake and supplementation with vitamins B6, B12, and folate.
Alkaptonuria

**Cause:** Defect in Homogenistic Acid Oxidase.

**Characteristic symptoms:**
- Homegenistic Urea
- Large joint arthritis
- Black pigmentation in cartilage and collagenous tissue.

**Treatment:** Diets low in phenylalanine and tyrosine.
Inborn errors of amino acid metabolism

Alkaptonuria
Aspartylglucosaminuria
Methylmalonic acidemia
Maple syrup urine disease
Homocystinuria
Tyrosinemia
Trimethylaminuria
Hartnup disease
Biotinidase deficiency
Ornithine carbamoyltransferase deficiency
carbamoyl-phosphate synthase I deficiency
disease
Citrullinemia
Hyperargininemia
Hyperhomocysteinemia
Hyperlysinemias
Nonketotic hyperglycinemia
Propionic acidemia
Hyperprolinemia
Conversion of Amino Acids to Specialized Products

First Lecture

Second lecture

Third Lecture

- Coenzymes
- Neurotransmitters
- Phospholipids
- Porphyrins
- Purines
- Pyrimidines
- Other nitrogenous compounds