NORADRENERGIC NEUROTRANSMISSION:
NOREPINEPHRINE BIOSYNTHESIS

PC/MC Objective: Know all of the steps on norepinephrine (NE) biosynthesis as shown on the next page: (also see CB Notes)

PC/MC Objective: Fully understand the first step in the biosynthesis of NE

- What is the substrate for this reaction? What is the product? Tyr -> L-DOPA
- How is this precursor substrate accumulated in NE nerves? Aminoacid uptake
- What is the enzyme required for the conversion of tyrosine to L-DOPA? TH
- Which cofactors are required for the conversion of tyrosine to L-DOPA? THF
- What role does tyrosine chirality play in the formation of L-DOPA? L-aas
- Describe the stereochemistry of this reaction (regiospecificity)? 3-OH
- Describe the kinetic significance of this reaction? Rate-limiting step
- In which portion of the NE nerve does this reaction occur? Cytoplasm

PC/MC Objective: Fully understand the second step in the biosynthesis of NE:

- What is the substrate for this reaction? What is the product? L-DOPA -> DA
- What is the enzyme required for the conversion of L-DOPA to DA? L-AAAD
- Which cofactors are required for the conversion of L-DOPA to DA? PLP
- What role does L-DOPA chirality play in the formation of DA? Essential
- Describe the stereochemical outcome of this reaction? Chirality lost!
- Describe the kinetic significance of this reaction? Not rate-limiting!
- In which portion of the NE nerve does this reaction occur? Cytoplasm
- Is this enzyme specific for L-DOPA? No. All Aromatic amino acids

PC/MC Objective: Fully understand the third step in the biosynthesis of NE:

- What is the substrate for this reaction? What is the product? DA -> NE
- What is the enzyme required for the conversion of DA to NE? DA-β-H
- Which cofactors are required for the conversion of DA to NE? Ascorbic acid
- Describe the stereochemical outcome of this reaction? R-NE only!
- Describe the kinetic significance of this reaction? Final step: NT formation
- In which portion of the NE nerve does this reaction occur? Vesicle

PC/MC Objective: NE as a hormonal precursor:

- For which other hormonal substrate is NE a precursor? E
- What is the substrate for this reaction? What is the product? NE -> E
- What is the enzyme required for the conversion of NE to E? PNMT
- Which cofactors are required for the conversion of NE to E? SAM
- In which tissue(s) is E formed? Adrenals
- How is this enzyme regulated? Hormones
NE BIOSYNTHETIC SCHEME

**Cyttoplasmic**

**Cofactor:** S-Adenosylmethionine (SAM)
**Enzyme:** Dopamine beta-hydroxylase
**Cofactor:** PLP

**Cytoplasmic**

**Cofactor:** O2, Fe^{2+}, THF
**Enzyme:** Tyrosine Hydroxylase
**Rate-limiting step**
**Regiospecific hydroxylation**

**Vesicular Membrane**

**Enzyme:** L-Aromatic Amino Acid Decarboxylase (L-AAAD)
**Cofactor:** Pyridoxal Phosphate (PLP)

**L-Tyrosine**

\[ \text{HO} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{NH}_2 \quad \text{COOH} \]

**L-DOPA**

\[ \text{HO} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{NH}_2 \quad \text{COOH} \]

**R-Norepinephrine (NE)**

\[ \text{HO} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{NH}_2 \]

**Epinephrine (E)**

\[ \text{HO} \quad \text{OH} \quad \text{H} \quad \text{NHCH}_3 \]

**Dopamine (DA)**

\[ \text{HO} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{NH}_2 \]
MC Objective: Based on fundamental metabolic principles, propose a mechanism for the enzyme-catalyzed formation of L-DOPA from tyrosine.

**Substitution at electronic rich 3-position (similar to aromatic hydroxylation)**

MC Objective: Based on fundamental metabolic principles, propose a mechanism for the enzyme-catalyzed formation of DA from L-DOPA:

![Diagram](image-url)
MC Objective: Based on fundamental metabolic principles, propose a mechanism for the enzyme-catalyzed formation of NE from DA:

\[
\text{Dopamine (DA)} \xrightarrow{\text{Conversion}} \text{R-Norepinephrine (NE)} \quad \text{(Stereospecific)}
\]

MC Objective: Based on fundamental metabolic principles, propose a mechanism for the enzyme-catalyzed formation of E from NE:

\[
\text{R-Norepinephrine (NE)} \xrightarrow{\text{PNMT}} \text{R-Epinephrine (E)}
\]

MC Objective: Generally describe how a dietary deficiency in certain vitamins or cofactors could adversely impact NE biosynthesis and lead to pathology. **Example.** A pyridoxine deficiency leads to a PLP deficiency and decreased conversion of L-DOPA to DA.

MC Objective: Generally describe how a genetic disease resulting in impaired or faulty enzyme biosynthesis could adversely impact NE biosynthesis and lead to pathology. **Example:** DA-β-H genetic deficiency results in inability to form NE from DA (can treat with L-DOPS as shown below).

MC Objective: Describe how administration of the following substances ("drugs") could enhance NE biosynthesis:

- Tyrosine (Tyrosine hydroxylase substrate)
- L-DOPA
- L-DOPS

MC Objective: Describe general circumstances in which the substances ("Drugs" above may be used. **L-DOPS for DA-β-H deficiency. L-DOPA as a DA precursor for treatment of Parkinsonism.** (see next page)
SUMMARY OF THE PHARMACOLOGIC ACTIONS OF L-DOPA

Oral Administration

GI TRACT LUMEN

Absorption

GI TRACT MEMBRANES

PLASMA

Peripheral L-AAAD

Peripheral COMT

KIDNEY

Elimination

BLOOD BRAIN BARRIER

Peripheral L-ADD

L-DA Side Effects

AA Uptake

NE

NERVE

LAAAD Storage

NE

DA

NE

DBH

Release

NE
MC Objective: Describe how administration of the following substances ("drugs") could inhibit NE biosynthesis: **Metyrosine (MeT) is a TGH inhibitor. Carbidopa is an L-AAAD inhibitor**

![Metyrosine and Carbidopa structures]

MC Objective: The biochemical mechanism of action for Carbidopa is shown below. What role does carbidopa structure play in expression of this activity? **Overall structure allows for binding to L-AAAD. Hydrazine group allows for binding to cofactor on the surface of the enzyme**

![Carbidopa mechanism diagram]

MC/PC Objectives: When would the drugs above be used as therapeutic agents?

**MeT: Potential antihypertensive; Carbidopa adjunct to L-DOPA therapy in Parkinsonism (see later notes)**

MC Objective: The drug shown below (α-methylDOPA) is an L-AAAD inhibitor and when converted to α-methyl-NE can function as a "false neurotransmitter" and a presynaptic α2-agonist.

- Describe the biochemical mechanism for L-AAAD inhibition
- Describe what the phrase "false neurotransmitter" means

![α-methylDOPA and α-MethylNE structures]
• The drug α-methylDOPA is an "amphoteric compound", and as such is difficult to formulate and not well absorbed from the GI tract. What does this mean?

• Methyldopate HCl is a water soluble prodrug form of α-methylDOPA. Explain why this derivative is more water soluble than the parent drug (see below).

• Explain the prodrug function of Methyldopate HCl. Why does this prodrug approach yield a drug capable of penetrating and expressing its activity in the CNS?

SEE NEXT PAGE FOR SUMMARY SHEET ON THE ACTIONS OF METHYLDOPATE!
SUMMARY OF THE PHARMACOLOGIC ACTIONS OF METHYLDOPATE

Methyldopate HCl → Oral Administration

GI TRACT LUMEN

Absorption

GI TRACT MEMBRANES

Esterases

α-Methyldopa

AA Uptake

LIVER

Plasma Esterases

PLASMA

BLOOD BRAIN BARRIER

NE

α-MeNE

log Dose

Response

Release

α-MeNE: False Transmitter

NE

α-MeNE

Storage