NOREPINEPHRINE METABOLISM (CATABOLISM)

MC/PC objectives: Describe the primary intra-neuronal and extra-neuronal pathways of NE catabolism: (CB Notes)

- What is the primary intra-neural metabolic pathway for NE metabolism? MAO
- What is the enzyme and cofactor that catalyze the intra-neural metabolic pathway of NE metabolism? Enzyme: MAO, Cofactor: Riboflavin
- What are the structural requirements for substrate (NE-like) activity for this enzymatic pathway? Ar-CH$_2$NH$_2$ optimal structure
- What is the name and structure of the product formed by the intra-neural metabolic pathway of NE metabolism? See Figure on next page
- What is the mechanism for the intra-neural metabolic pathway of NE metabolism?
- What is the physiologic significance of this metabolic pathway? Eliminates amino group and therefore agonist activity of NE (terminates NE NT)

- What is the primary extra-neuronal metabolic pathway for NE metabolism? COMT
- What is the enzyme and cofactor that catalyze the extra-neural metabolic pathway of NE metabolism? Enzyme: COMT, Cofactor is SAM
- What are the structural requirements for substrate (NE-like) activity for this enzymatic pathway? Catechol group is key functionality
- What is the name and structure of the product formed by the extra-neural metabolic pathway of NE metabolism? See Figure on next page
- What is the mechanism for the extra-neural metabolic pathway of NE metabolism?
- What is the physiologic significance of this metabolic pathway? Eliminates the free catechol group and reduces agonist activity of NE (terminates NE NT)

- What secondary (oxidative and reductive) metabolic pathways may the aldehydes formed during NE metabolism undergo? See Figure on next page
- Which enzymes catalyze these secondary pathways? ADH and AR

- Outline the metabolic sequence whereby the end products of NE metabolism including 3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxy-phenylethleneglycol are formed. See Figure on next page
NE CATABOLISM: INTRA- AND EXTRA-NEURONAL PATHWAYS

1. Uptake in presynaptic nerve (U-1)
2. Enzyme: Monoamine Oxidase (MAO)
   Cofactor: Riboflavin
   (Intra-neuronal: Mitochondria)

1. Uptake by non-NE-nerves (U-2)
2. Enzyme: Catecholamine-O-Methyltransferase (COMT)
   Cofactor: S-adenosylmethionine (SAM)
   (Extra-neuronal)

(Regio-selective methylation)

3,4-Dihydrophenylglycolaldehyde

3,4-Dihydromandelic Acid  3,4-Dihydrophenylethylene glycol

Catecholamine O-methyltransferase (COMT)

3-Methoxy-4-hydromandelic Acid  3-Methoxy-4-hydrophenylethylene glycol

1. MAO
2. Aldehyde Dehydrogenase

1. MAO
2. Aldehyde reductase

Urinary Metabolites

1. Uptake by tissues with MAO
2. MAO metabolism
3. Subsequent Metabolism
MC Objective: What is the mechanism by which MAO catalyzes deamination of NE and NE-like compounds? Identify the substrate, enzyme and cofactor in the figure below:

MC Objective: Based on this mechanism, what are the optimal structural requirements for substrate activity (RCH$_2$NH$_2$ in the figure below)

MC Objective: What physiologic effects would result from inhibition of MAO?

SEE FURTHER QUESTIONS ON MAO INHIBITORS LATER IN THIS SECTION!

**MONOAMINE OXIDASE (MAO) MECHANISM**

*Summary of the MAO-Catalyzed Reaction:*

Dopamine $\xrightarrow{1e^-}$ Imine Intermediate $\xrightarrow{\text{H}^+}$ Aldehyde Product
MC Objective: What is the mechanism by which COMT catalyzes methylation of NE and NE-like compounds? Identify the substrate, enzyme and cofactor in the figure below.

MC Objective: Based on this mechanism, what are the optimal structural requirements for substrate activity? *Catechol (3,4-diOH) linked to ethylamine*

MC Objective: What physiologic effects would result from inhibition of COMT? *Incr NE*

SEE FURTHER QUESTIONS ON COMT INHIBITORS LATER IN THIS SECTION!

MC Objective: What is the mechanism by which aldehyde dehydrogenase (oxidase) and aldehyde reductase catalyze oxidation and reduction of the aldehyde intermediates formed from the MAO-metabolism of NE and NE-like compounds? Which cofactors would be required for these reactions?
MC/PC Objective: What are the primary isozymes of MAO, where are they located and what are their substrate specificities? (CB Notes)

- What is MAO-A and MAO-B? See below
- What is the physiologic role of these MAO isozymes? Inactivate bioactive amines!
- Where are these isozymes found? See below
- Are these enzymes selective in their substrate specificities? Do they deaminate all biogenic amines (NE, DA, 5-HT)? See below

MAO-A preferentially deaminates epinephrine, norepinephrine, and serotonin, while MAO-B metabolizes benzylamine and phenylethylamine. Dopamine and tyramine are metabolized by both isozymes. In neural tissues, this enzyme system regulates the metabolic decomposition of catecholamines and serotonin. Hepatic MAO inactivates circulating monoamines or those that are introduced via the GI tract into portal circulation (eg, tyramine).

**MAO Substrate Specificity**

![MAO Substrate Specificity](image)

MC/PC Objective: What classification schemes are used to categorize the MAO Inhibitors (MAOIs)?

- MAOI generation: 1st, 2nd, 3rd.
- MAOI structure: propargylamines, hydrazines/hydrazides, cyclopropylamines, aminethylbenzamides
- MAOI specificity: MAO-A versus MAO-B
MC/PC Objective: List the primary 1st generation MAOIs and characterize them by structure and MAO selectivity:

- Non-selective MAOI products; **Inhibit MAO-A and MAO-B**
- Consist of propargylamines, hydrazines/hydrazides and cyclopropylamines

![Chemical structures](Phenelzine, Iproniazid, Isocarboxazid, Nialamide, Tranylcypromine, Pargyline)

MC/PC Objective: List the primary 2nd generation MAOIs and characterize them by structure and MAO selectivity:

- "Semi-selective" MAOI products: **See products below**
- Consist of propargylamines

![Chemical structures](Selegiline (Deprenyl): MAO-B Selective, Chlorgyline: MAO-A Selective)

MC/PC Objective: List the primary 3rd generation MAOIs and characterize them by structure and MAO selectivity: **You are not responsible to know about these compounds on the exam (3rd generation agents are experimental)**

- "Semi-selective" MAOI products
- Consist of aminoethylbenzamides and analogues

![Chemical structures](Meclobenide: MAO-A Selective, Bromfaromine: MAO-A Selective, RO-19-6327: MAO-B Selective)
MC/PC Objective: Describe the mechanism whereby various structural types of MAOIs inhibit MAO:

- Why are many of these compounds called "suicide" or "mechanism"-based inhibitors? **They are converted to reactive intermediates by the normal enzyme-catalyzed reactions and these chemical react (form a covalent bond with MAo and thereby inactive MAO**

**MECHANISM OF MAO INHIBITION BY CYCLOPROPYLAMINES**

**MECHANISM OF MAO INHIBITION BY PROPARGYLAMINES**

MC/PC Objective: What other pharmacologic actions do some of the MAOIs express? **They have the potential to potentiate all biogenic amine (NE, DA and 5-HT) neurotransmission.**
MC/PC Objective: Based on their MAO selectivity pattern, which compounds would have utility in the treatment of depression and Parkinsonism and why?

- Which specific MAOI is indicated for the treatment of Parkinsonism? **Selegilene**
- Is this drug used alone or in combination with other agents? **With L-DOPA**

MC/PC Objective: Generally characterize the pharmacokinetic and biodisposition profiles of the MAOIs?

- Are they orally effective? Why? **YES! Sufficiently stable, water soluble (dissolve) and lipophilic to be absorbed**
- Do they distribute adequate to target tissue areas? **Sufficiently lipophilic to penetrate the BBB and enter the CNS**
- Explain why even though peak levels of MAOI are reached in 2-3 hours, the maximal inhibition of MAO does not occur until 5 -10 days of initiation of therapy? **Think!**
- Why are the "effective half-lives" of the MAOIs greater than their plasma half-lives? **They form long-lasting covalent complexes with the target enzyme (MAO) which persist long after drug is cleared from plasma!**
- Simple hydrazine derivatives such as phenelzine is subject to "genetically variable" metabolism by acetylation. Describe this pathway and the significance of variability?

![Phenelzine](image1.png)

**Phenelzine**    
**N-Acetyl Metabolite**

- Selegilene is chiral and has been marketed as the racemate and the pure R-enantiomer. What is the significance of this based on its metabolic profile?

![Selegilene](image2.png)

**Selegilene**  
(R- and S-enantiomers possible)

**Methamphetamine**

- Reduction of MAO Activity
- CNS stimulant activity with S-isomer

*SEE MAOI SUMMARY SHEEET ON NEXT PAGE*
SUMMARY OF THE PHARMACOLOGIC ACTIONS OF THE MAOIs

**Oral Administration**

**Absorption**

**GI MEMBRANES**

**Metabolism**
- N-Acetylmethabolite (Less Active)
  - LIVER
  - Metabolism (Oxidation)
    - OND metabolite (Less Active)

**Metabolism (Acetylation)**

**SIDE EFFECTS:**
- Inhibition of peripheral MAOs in gut (B) and nerves (A)

**BLOOD-BRAIN BARRIER**

**Uptake-1**

**NERVE**

- MAOI
- MAOI*
- MAOI
- MAO
- MAO
- MAO
- MAO
- MAO

**NERVE**

- Covalent Complex
- "Reactive" MAOI
- Initial complex

(See notes for structures!)
MC/PC Objective: Describe why the therapeutic utility of the MAOIs, particularly the “older” MAOIs, is limited by their adverse reaction and drug interaction profiles.

- Why should tyamine-containing foods not be ingested by patients on MAOI therapy. What is "tyramine" and in which foods is it found? What effects may an MAOI have on tyramine and what is the physiologic consequence?

- What is the general adverse reaction profile for the MAOIs and what is the general neurochemical basis for these?

- Why should MAOIs not be used concurrently with the following drugs?
  - Tricyclic antidepressants
  - SSRIs
  - Antihistamines
  - Anticholinergics
  - L-DOPA
MC/PC Objective: Which COMT inhibitor products (COMTIs) are currently available and how do they express their biochemical mechanism?

- Characterize the biochemical mechanism of action of the COMTIs? **Competitively inhibit the binding of NE to CMT and thereby slow this pathway of NE metabolism**

- What role does COMTI structure play in biochemical activity? **The nitrocatechol group allows for higher binding than NE by COMT**

- Why are COMTIs used in combination with L-DOPA and carbidopa to treat Parkinsonism? **To slow the rate of peripheral metabolism of L-DOPA by COMT to pharmacologically inactive metabolites (3-OMD).**

- How does COMTI therapy increase L-DOPA bioavailability and decrease the formation of 3-OMD? What is the significance of this? **See Figure**

- Explain why tolcapone penetrates the blood-brain barrier and inhibits COMT both peripherally and centrally, while entacapone’s actions are limited to the periphery? **It is more lipophilic**

- What are the common adverse reactions of the COMTIs and how are these related to the biochemical actions of these drugs? **They can inhibit the metabolism of all catechols**
• Explain why the COMTIs may potentiate the chronotropic and arrhythmogenic effects of IV administered isoproterenol and epinephrine? What other drugs may these compounds interact with? Isoproterenol and epinephrine are also catechols and are MORE DEPENDENT on COMT for metabolism than NE. Thus COMTIs will prolong the actions of these drugs when used concurrently.

• Why should COMTIs use be avoided with non-selective MAO inhibitors such as phenelzine, tranylcypromine? Because non-selective MAOs and COMTIs used together would block both (all) pathways of biogenic amine metabolism.

• Why may entacapone may be taken concomitantly with selective MAO-B inhibitors such as selegiline?

• Entacapone (with the E-configuration) is metabolized to the Z-isomer in the plasma and RBCs. What is the structure of the Z-isomer and would this isomer be expected to contribute significantly to clinical activity? Z_isomer is less active

![Entacapone (E) and Z-Isomer](image)

• Tolcapone and Entacapone (and Z-entacapone) undergo hepatic glucuronidation. What are the structures of these metabolites and what is the significance of their formation?

![Tolcapone/Entacapone and Inactive Glucuronide Conjugate](image)
SUMMARY OF THE PHARMACOLOGIC PROFILES OF THE COMTis

**Oral Administration**

- **GI MEMBRANES**
  - Entacapone
  - Tolcapone

- **Absorption**
  - Metabolism
  - **LIVER**
    - 3-OMeNE or 3-OMeDA
    - Peripheral COMT
    - NE or DA

- **BLOOD-BRAIN BARRIER**
  - 3-OMeNE

- **NERVE**
  - L-Tyr → L-DOPA → DA → DA → NE
  - MAO
  - Uptake-1

- **Diffusion or Uptake-2**
  - NE
PROBLEM SET

1. Analyze the structures of the compounds shown below and circle the appropriate response or responses. There may be more than one correct answer, or no correct answer (“None”):

   ![Compounds A, B, and C]

   a. Which compounds are chiral?.........................................................A B C None
   b. Which compounds are predominantly ionized in plasma?..............A B C None
   c. Which compounds express their activity by action in the CNS?....A B C None
   d. Which compounds express their activity by enzyme inhibition?....A B C None
   e. Which compounds can block the metabolic breakdown of NE?....A B C None
   f. Which compounds inhibit the biosynthesis of NE?...............A B C None
   g. Which compounds may be metabolized by methyl conjugation?...A B C None
   h. Which compounds may be metabolized by cytochrome OND?.....A B C None
   i. Which compounds are reversible inhibitors of MAO-B?...........A B C None
   j. Which compounds may be metabolized by COMT?..................A B C None
   k. Which compounds are inactivated by OND metabolism?........A B C None
   l. Which compounds may react with pyridoxal phosphate?...........A B C None
   m. Which compounds are orally active?.................................A B C None
   n. Which compounds enhance the efficacy of L-DOPA?..............A B C None