DRUGS THAT ALTER DOPAMINE NERVE STRUCTURE OR FUNCTION

MC Objective: Characterize the chemical and pharmacologic properties of "DA releasers" such as Amantadine and the amphetamines)

- Amantadine is a basic amine (pKa 10.8) and predominantly ionized at physiologic pH.
- Amantadine has a lipophilic carbon "cage structure" that enhances tissue penetration and sterically blocks metabolism (no AMO or other deamination metabolism)
- Amantadine promotes DA release from presynaptic nerves (activity is dependent on intact and functional DA nerves. Its activity is enhanced when administered with L-DOPA (greater DA formation)!
- Amantadine also delays the reuptake of DA in functional DA nerves
- Amantadine has a rapid onset : within 2 weeks
- Amantadine has lower efficacy (because of its mechanism of action) but fewer side effects that L-DOPA
- Amantadine is eliminated unchanged renally and therefore should be used with caution in renal impairment (reduce dose!)
- Amphetamines (see structures below) can release DA, as well as inhibit DA reuptake and weakly block MAO metabolism by competitive inhibition this enzyme.

MC Objective: Characterize the chemical and pharmacologic properties of inhibitors of DA release (GHB and its lactone)

- GHB and its lactone form specifically block DA release (not other NTs) by an unknown mechanism
- This drug, particularly in its lipophilic lactone form can pass biologic membranes including the BBB
MC Objective: Characterize the chemical and pharmacologic properties of the natural product Reserpine (from *Rauwolfia serpentina*), a DA depletor

- Reserpine depletes NE from dopaminergic (and adrenergic and serotonergic nerves) by inhibiting the Mg-ATPase transporter responsible for sequestering DA (and NE and 5-HT) in storage vesicles. The DA not stored is largely metabolized by MAO. This results ultimately in depletion of intraneuronal stores of neurotransmitter.
- Based on its mechanism of action, reserpine has been used for the treatment of schizophrenia and hypertension.
- Reserpine is used only infrequently now because its non-specific actions result in an array of undesired peripheral and central side effects.
- Reserpine in solution may undergo hydrolysis, indole decomposition (light-mediated) and epimerization. Show the epimerization product and why it occurs.
- Reserpine readily passes the BBB by diffusion and enters the CND due to its lipophilicity.
- Why does the duration of action of reserpine exceed its plasma half-life?
- Reserpine is metabolized by esterase-mediated hydrolysis and oxidative O-demethylation. Propose structures for these metabolites.

MC Objective: Characterize the chemical and pharmacologic properties of the inhibitors of DA reuptake: **Note that the structures required to block DA reuptake differ significantly from those required to block NE or 5-HT reuptake!**
Many of these drugs have multiple pharmacologic actions (amphetamines and cocaine) in addition to inhibition of DA reuptake.

Cocaine primarily is a drug of abuse that has a short half-life due to rapid metabolic inactivation by ester hydrolysis and OND.

The actions of some of the DA reuptake inhibitors (Bupropion and Nomifensine) will be covered in more when inhibition of NT reuptake is discussed generally.

**MC Objective:** Characterize the chemical and pharmacologic properties of compounds capable of destroying DA neurons.

- 6-Hydroxydopamine and xylamine are DA depletors in PNS (except the adrenal medulla) and CNS
- Irreversibly destroy sympathetic and DA neurons via formation of reactive metabolites that are capable of alkylating nucleophilic residues on nerve enzymes and proteins and rendering the nerve non-functional:

![Chemical Destruction of DA nerve terminals](image)

- MPTP is a by-product or contaminant in the synthesis of the narcotic MPPP (meperidine analogue referred to as "designer heroin")
  1. MPTP binds selectively to MAO-B which is highly concentration in the SN
  2. Glial and 5-HT cells convert MPTP to MPDP+ which can diffuse iout an disproportionate to MPP+
  3. DA and NE terminals accumulate MPP+ through catecholamine uptake.
  4. Neuromelanin of SN neurons bind MPP+
  5. MPP+ rapidly accumulates in mitochondria where it inhibits NADH dehydrogenase resulting in ATP depletion and cell death
Bioactivation of MPPP and DA Neuronal Death

MPPP
("Designer heroin")

Elimination
-OOCC₃H₇

MAO-B

H₂O

MPP⁺

H₂O

MAO-B

MPDP⁺