DOPAMINE RECEPTOR AGONISTS

**MC Objective:** Describe how modification of the structure of dopamine alters dopamine receptor affinity:

- **N-Methyl Subst**: DA > Phenethylamines and other Non-catechols
- **Beta-OH Subst**: DA >> Amides and other non-primary amines
- **Alpha-Me Subst**: Epine = DA
- **Remove OHs**: NE: 20X < DA
- **Alter NH₂**: Alpha-MeDA < DA

**MC Objective:** What factors limit the therapeutic utility of DA as a drug?

- Lack of dopaminergic receptor selectivity: adverse reactions
- Lack of metabolic stability (MAO, COMT): short duration
- Lack of oral bioavailability due to polarity and rapid first pass metabolism
- Inadequate distribution to target tissues (CNS for Parkinsonism)
MC Objective: Describe the structural relationship between the aporphines and dopamine. Also describe the pharmacologic properties of the aporphines.

- The aporphines are \textbf{conformationally restricted} analogues of DA as shown above.
- Isoapomorphine represents the trans-$\beta$-rotamer of DA and is \textit{inactive} as a DA agonist.
- 1,2-Dihydroxyaporphine represents the cis-$\alpha$-rotamer and is \textit{inactive} as DA agonist.
- Apomorphine represents the trans-$\alpha$-rotamer of DA. It is obtained from acid-catalyzed rearrangement of morphine.
- Apomorphine is more lipophilic than DA and can penetrate the BBB.
- Apomorphine is a potent D-1 and D-2 receptor agonist.
- Apomorphine has anti-Parkinson activity (= L-DOPA), but its powerful emetic (medullary actions) limit its therapeutic potential.
- N-propyl-apomorphine is active only as a presynaptic D-2 agonist (not an agonist at post-synaptic D-2 receptors) and is 2-90X as active as apomorphine.
MC Objective: How do DA agonists compare to L-DOPA in the treatment of Parkinsonism? What advantages may dopamine agonists offer over L-DOPA:

- DA agonists do not require bioactivation like L-DOPA: They are active as is!
- DA agonists do not require co-administration of an L-AAAD inhibitor (Carbidopa), MAO inhibitor (Selegilene) or COMT inhibitor (entacapone or tolcapone)
- DA agonists do not require the presence of intact nigrostriatal DA neurons.
- DA agonists are longer acting than L-DOPA due primarily to a slower rate of metabolic inactivation.
- Peripheral and CNS side effects similar to L-DOPA

MC Objective: Describe the chemical and pharmacologic properties of the ergot and ergopeptide DA agonists

- The ergots derivatives consist of an ergoline ring system. This ring system contains the basic structural elements of dopamine and apomorphine which allow for dopamine receptor binding.

- Pharmacologic Properties

  - Bromocriptine is a D-2 agonist/D-1 partial antagonist. Thus it has use in mild to moderate Parkinsonism and Amenorrhea/galactorrhea/female infertility. As adjunctive treatment to levodopa, bromocriptine therapy may provide additional therapeutic benefits in those patients who are currently maintained on levodopa, and may permit reducing the maintenance dose of levodopa thus reducing adverse reactions associated with long-term levodopa therapy (see Pharmacology notes).

  - Pergolide is a long-acting D-1 and D-2 agonist. It is 10 to 1000 times more potent than bromocriptine on a mg per mg basis. Pergolide inhibits the secretion of prolactin; it causes a transient rise in serum concentrations of growth hormone and a decrease in serum concentrations of luteinizing hormone. In Parkinson's disease, pergolide is used as adjunctive treatment with levodopa/carbidopa.
Pharmacokinetic Properties

- Bromocriptine has very low oral bioavailability due to BOTH poor absorption (too lipophilic!) and extensive first pass metabolism. The majority of the drug is eliminated in feces as metabolites.

- Pergolide has higher oral bioavailability than bromocriptine (ca. 60%). At least 10 metabolites have been detected, including N–despropylpergolide, pergolide sulfoxide and pergolide sulfone. Pergolide sulfoxide and sulfone are dopamine agonists in animals. The major route of excretion is renal.

MC Objective: Describe the chemical and pharmacologic of the non-ergoline/non-apomorphine DA-Agonists used for Parkinsonism:

These drugs contain the basic structural elements of dopamine and apomorphine which allow for dopamine receptor binding. These drugs may display greater receptor selectivity than the ergots derivative described above.

### Receptor Binding Profile of the DA Agonists used in Parkinsonism

<table>
<thead>
<tr>
<th>DA Agonist</th>
<th>DA</th>
<th>NE</th>
<th>5-HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromocriptine</td>
<td>D-2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pergolide</td>
<td>D-2&gt;D-3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>D-3&gt;D-2&gt;D-4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>D-3&gt;D-2&gt;D-4</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Properties of Ropinirole HCl:

- D-2 agonist (presyn) and D-3: D-3>D-2
- DA receptor affinity = apomorphine, but less stereotypic behavior
- Little or no alpha-1. Alpha-2 or beta-receptor activity, or 5-HT, BDZ, GABA, ACH or opioid receptors
- Less dyskinesias and fewer “on/off” fluctuations
- Little tolerance development
- Monotherapy for early PD or L-DOPA combo for late PD
- Lower/variable oral bioavailability (first pass)
- Extensive metabolism by AH and OND (Cytochrome enzymes)
• **Properties of Pramipexole diHCl:**
  - Chiral: Active S-isomer marketed
  - Direct D-2 agonist and D-3: 7X higher D-3 affinity > D-2, D-4>>D-1
  - Low alpha receptor and 5-HT receptor affinity
  - Antioxidant action: Protects from L-DOPA toxicity
  - Use: Monotherapy for early PD; with L-DOPA for late PD
  - Higher oral bioavail (90%)
  - Minimal metabolism
  - Eliminated renally unchanged

**MC Objective:** Describe the chemical and pharmacologic of the Fenoldopam mesylate:

![Fenoldopam mesylate](image)

• Fenoldopam is a racemic mixture with the R-isomer responsible for the biological activity. The R-isomer has » 250–fold higher affinity for D1–like receptors than does the S-isomer.

• D-1 agonist activity results in vasodilation (in renal and other tissues) which is useful in the treatment of hypertensive emergencies

• Also has some alpha-2 agonist activity, but minimal affinity for other adrenergic, 5-HT or ACh receptors

• Administered by continuous IV infusion. Fenoldopam is too poorly absorbed (too polar) and too rapidly metabolized to be orally effective (not practical for indication anyway!)

• Approximately 90% of infused fenoldopam is eliminated in urine (10% in feces) with only 4% of the dose excreted unchanged. The principal routes of metabolism involve conjugation by COMT methylation, glucuronidation and sulfation.
SUMMARY OF DRUGS THAT ALTER DA NEUROTRANSMISSION

DA AGONISTS
- Dopamine (D1-D5)
- Apomorphine (D1, D2)
- Bromocriptine (D1, D2)
- pergolide (D1, D2)
- Ropinodle (D2, D3)
- Pramipexole (D2,D3)
- Fenoldopam (D1)

DA ANTAGONISTS
- Phenothiazines
- Thioxanthenes
- Butyrophenones
- Dibenzoazepines
- Indolines
- Diphenybutylpiperidines
- Benzamides
- Benzisoxazoles

Hydrazines: Iproniazid, Phenelzine
Propargylamines: Selegilene
MAOIs
- Propargylamines: Selegilene
- Hydrazines: Iproniazid, Phenelzine
- COMT: Tolcapone, Entacapone
- MAO: MAO inhibitors
- ETC: Entacapone, MAO inhibitors
- COMT: Tolcapone, Entacapone
- DA Rec: dopamine reuptake inhibitors