Parkinsonism

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Parkinson’s disease (PD) is a degenerative, progressive neurologic disorder characterized by lesions of the basal ganglia that produce abnormalities in motor activities.

Clinical syndrome

- Tremor at rest
- Rigidity
- Ataxia
- Bradykinesia
- Disorder of consciousness, recognition, remembrance, and show dementia.
Etiology

- reduction in the activity of inhibitory dopaminergic neurons in the substantia nigra and corpus striatum parts of the brain's basal ganglia system that are involved in motor control. This results in a decrease in dopamine in these nerve tracts.

Causes:
1- Genetic factors do not play a dominant role.

2- Environmental factor

3- **Secondary parkinsonism**: viral encephalitis or multiple small vascular lesions.

4. Drugs such as the phenothiazines and *haloperidol*, that block dopamine receptors in the brain' may also produce parkinsonian symptoms.

5- Iatrogenic parkinsonism
2 Loss of the inhibitory effect of dopamine results in more production of acetylcholine, which triggers a chain of abnormal signaling leading to impaired mobility.

Connections to muscle through motor cortex and spinal chord

1 Cell death results in less dopamine release in the neostriatum.

**Figure 8.6**
Role of substantia nigra in Parkinson's disease. DA = dopamine; GABA = γ-aminobutyric acid.
**Substantia nigra:** is the source of dopaminergic neurons that terminate in the striatum that fire tonically.

**Neostriatum:**
- the neostriatum is connected to the substantia nigra by neurons that secrete the inhibitory transmitter GABA at their termini in the substantia nigra.
- cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini.
- This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas.
- In Parkinson disease, destruction of cells in the substantia nigra results in the degeneration of neuron responsible for secreting dopamine in the neostriatum.
- Thus, the normal modulating inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction of acetylcholine. This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.
Strategies in Treatment

- The symptoms of parkinsonism due to:
- an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

- **Therapy is aimed at:**
- A- restoring dopamine in the basal ganglia.
- B- antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.
Levodopa and carbidopa

*Levodopa* is a metabolic precursor of dopamine.

- It restores dopamine levels in the extrapyramidal centers (substantia nigra) that atrophy in parkinsonism.

- In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra is adequate for conversion of *levodopa* to dopamine. Thus, the patient rarely complains that the drug effects "wear off."

- With time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops.
**Mechanism of action**

**Levodopa:** Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, levodopa, is readily transported into the CNS and is converted to dopamine in the brain.
- Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension.

**Carbidopa:** The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa, a dopa decarboxylase inhibitor that does not cross the blood-brain barrier.

Carbidopa diminishes the metabolism of levodopa in the gastrointestinal (GI) tract and peripheral tissues; thus, it increases the availability of levodopa to the CNS.

The addition of carbidopa:
1. lowers the dose of levodopa needed by four- to five-fold
2. decreases the severity of the side effects of peripherally formed dopamine
Figure 8.7
Synthesis of dopamine from levodopa in the absence and presence of carbidopa, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.
2. **Actions:** *Levodopa* decreases the rigidity, tremors, and other symptoms of parkinsonism.

3. **Therapeutic uses:**

*Levodopa-carbidopa* treatment reduces the severity of the disease for the first few years of treatment.

4. **Absorption and metabolism:**

- The drug is absorbed rapidly from the small intestine (when empty of food).

- *Levodopa* has short half-life (one to two hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response ("on-off" phenomenon).

- Ingestion of meals with a high in protein content, interferes with the transport of *levodopa* into the CNS.

- Large, neutral amino acids (leucine and isoleucine) compete with *levodopa* for absorption from the gut and for transport across the blood-brain barrier.
Adverse effects:

Peripheral effects:
- GIT: Anorexia, nausea, and vomiting occur because of stimulation of the emetic center.
- CVS: Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop.
- Eye: Adrenergic action on the iris causes mydriasis,
- Blood: blood dyscrasias and a positive reaction to the Coombs test.
- Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.

CNS effects:
- Flactuation in response (on-off phenomenon)
- Visual and auditory hallucinations.
- abnormal involuntary movements (dyskinesia) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia.
- Levodopa can also cause mood changes, depression, and anxiety.
Figure 8.9
Some drug interactions observed with levodopa.
Interactions:

• The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness.

• Concomitant administration of levodopa and monoamine oxidase (MAO) inhibitors, such as phenelzine, can produce a hypertensive crisis.

• In many psychotic patients, levodopa exacerbates symptoms, possibly through the buildup of central amines.

• In patients with glaucoma, the drug can cause an increase in intraocular pressure.

• Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias.

• Antipsychotic drugs are contraindicated in parkinsonian patients, because these block dopamine receptors and produce a parkinsonian syndrome themselves.
Dopamine receptor agonists

1- Ergot derivatives, *bromocriptine* and *pergolide*,

2- Non-ergot drugs, *ropinirole* and *pramipexole*.

**Advantages:**

- Have durations of action longer than that of *levodopa*

- Are effective in patients exhibiting fluctuations in their response to *levodopa*.

- less risk of dyskinesias and motor fluctuations when compared to patients started with *levodopa* therapy.
Bromocriptine and pergolide

*Bromocriptine* and *pergolide* both ergotamine (vasoconstrictor action) derivatives, are dopamine receptor agonists.

- *Pergolide* is the more potent of the two.
- The dose is increased gradually during a period of two to three months.

Side effects: Hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common than levodopa, whereas dyskinesia is less prominent.

- In psychiatric illness, they may cause the mental condition to worsen.
- In patients with a history of myocardial infarction cardiac problems may develop.
- In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and
- In patients with peptic ulcer, there is a worsening of the ulcer.
- have the potential to cause pulmonary and retroperitoneal fibrosis.
Pramipexole and ropinirole

- Pramipexole and ropinirole are non-ergot agonists at dopamine receptors.
- They alleviate the motor deficits in both levodopa-naive patients and patients with advanced Parkinson disease taking levodopa.
- They delay the need to employ levodopa therapy in early Parkinson, and may decrease the dose of levodopa in advanced Parkinson.

Unlike the ergotamine derivatives:

1- pramipexole and ropinirole do not exacerbate peripheral vasospasm, nor do they cause fibrosis.

2- Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side-effects of these drugs;

3- dyskinesias are less frequent than with levodopa.

4- pramipexole depend on renal function for its elimination, so, Cimetidine, which inhibits renal tubular secretion of organic bases, increases the half-life of pramipexole by forty percent.

5- The fluoroquinolone antibiotics shown to inhibit the metabolism of ropinirole.
<table>
<thead>
<tr>
<th></th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>&gt;90%</td>
<td>55%</td>
</tr>
<tr>
<td>$V_d$</td>
<td>7 L/kg</td>
<td>7.5 L/kg</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 hours$^1$</td>
<td>6 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Negligible</td>
<td>Extensive</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal$^2$</td>
</tr>
</tbody>
</table>

$^1$Increases to 12 hours in patients greater than 65 years old
$^2$Less than 10 percent excreted unchanged

Figure 8.13
Pharmacokinetic properties of dopamine agonists of pramipexole and ropinirole. $V_d$ = volume of distribution.
<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Pramipexole</th>
<th>Ropinirole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Insomnia</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Dizziness or light-headedness</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Hallucinations or confusion</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Orthostasis</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Nausea</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Constipation</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

+ = Incidence of 1 to 5 percent; 
++ = incidence of 6 to 15 percent; 
+++ = incidence of 16 to 25 percent; 
+++++ = incidence of greater than 25 percent.

**Figure 8.14**
Side effects of dopamine agonists pramipexole and ropinirole.
Amantadine

- It was accidentally discovered that the antiviral drug amantadine effective in the treatment of influenza.
- Amantadine increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type glutamate receptors.
- CNS: restlessness, agitation, confusion, hallucinations, and acute toxic psychosis.
- Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.

- Amantadine is less efficacious than levodopa, and Tolerance develops more readily.

- The drug has little effect on tremor, but is more effective than the anticholinergics against rigidity and bradykinesia.
Selegiline

selectively inhibits MAO B (which metabolizes dopamine), but does not inhibit MAO A (which metabolizes norepinephrine and serotonin).

Thus decreasing the metabolism of dopamine → increase dopamine levels in the brain.

- It enhances the actions of levodopa
- when administered together, it reduces the required dose of levodopa.

- If selegiline is administered at high doses, the selectivity of the drug is lost, and the patient is at risk for severe hypertension.

- Has a neuroprotective effect by suppressing the formation of oxidative metabolites of dopamine (antioxidant).
Catechol-O-methyltransferase inhibitors

• the methylation of levodopa by catechol-0-methyltransferase (COMT) to 3-0-methyldopa is a minor pathway for levodopa metabolism.

• when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-0-methyldopa is formed that competes with levodopa for active transport into the CNS.

• inhibition of COMT by entacapone or tolcapone leads to decreased plasma concentrations of 3-0-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.

• Both reduce the symptoms of "wearing-off" phenomena seen in patients on levodopa-carbidopa.

• Entacapone and tolcapone are nitrocatechol derivatives that selectively and reversibly inhibit COMT.
**Figure 8.11**

Effect of entacapone on dopa concentration in the central nervous system (CNS).

COMT = catechol-O-methyltransferase.
Oral absorption of both drugs occurs readily and is not influenced by food.

They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution.

*Tolcapone* penetrates the blood-brain barrier and inhibits COMT in the CNS.

*Tolcapone* has a long duration of action.

Both drugs are extensively metabolized.

Dosage may need to be adjusted in patients with moderate or severe cirrhosis.
Adverse effects

- Diarrhea, nausea, anorexia,
- Postural hypotension
- Dyskinesias, hallucinations, and sleep disorders

Fulminating hepatic necrosis is associated with tolcapone use.
The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy. 

**benztropine, trihexyphenidyl, and biperiden**

All these drugs can induce mood changes, xerostomia and visual problems.

They interfere with gastrointestinal peristalsis, and are contraindicated in patients with glaucoma, prostatic hypertrophy or pyloric stenosis.

Blockage of cholinergic transmission produced effects similar to augmentation of dopaminergic transmission.

Adverse effects are similar to those caused by high doses of atropine—for example, pupillary dilation, confusion, hallucination, urinary retention, and dry mouth.