Parkinson disease

Decreased amount of dopamine

Normal amount of acetylcholine
Parkinson's Disease
Parkinson’s disease

- Parkinson’s disease results from the degeneration of dopaminergic neurons in the substantia nigra
- These neurons project to other structures in the basal ganglia
- The basal ganglia includes the striatum, substantia nigra, globus pallidus and subthalamus
Parkinson’s disease

- Parkinson’s disease is characterized by resting tremor, rigidity, akinesia (difficulty in initiation of movement) and bradykinesia (slowness in the execution of movement).
- These symptoms are due to loss of function of the basal ganglia which is involved in the coordination of body movement.
Hoehn and Yahr Staging of Parkinson's Disease

- **Stage 1:** Mild signs and symptoms on one side only, not disabling but friends notice.
- **Stage 2:** Symptoms are bilateral, minimal disability, posture and walk affected
- **Stage 3:** Significant slowing, dysfunction that is moderately severe
- **Stage 4:** Severe symptoms, walking limited, rigidity, bradykinesia, unable to live alone
- **Stage 5:** Cachectic, complete invalidism, unable to stand, walk, require nursing care
Parkinson’s disease

- Resting tremor
- Rigidity
- Bradykinesia

• Results from degeneration of dopaminergic neurons
Aetiology

- Remain largely unknown
- Heredity have a limited role
- Defective gene responsible for a rare condition called autosomal recessive juvenile parkinsonism (teens and 20s)
- Oxidative stress theory (environmental origin)
Pathogenesis

- Dopaminergic neuron degeneration decreased activity in the direct pathway and increased activity in the indirect pathway
- As a result thalamic input to the motor area of the cortex is reduced and
- Patient exhibits rigidity and bradykinesia
- Inhibition of dopaminergic activity leads to excessive cholinergic activity
Neurotransmitter Imbalance

- Basal ganglia normally contains balance of dopamine and acetylcholine
- Balance necessary to regulate posture, muscle tone and voluntary movement
- In Parkinson’s, lack inhibitory dopamine and thus an increase in excitatory acetylcholine
Parkinson’s disease
(bradykinesia, akinesia, rigidity, tremor, postural disturbances)

Huntington’s disease
(hyperkinesia)
Anti-Parkinson drugs

- Drugs used are to increase levels of dopamine or to inhibit the actions of acetylcholine in the brain.
Treatment

- Drugs increase dopamine levels
  - Levodopa
  - Selegiline
  - Amantadine
  - Carbidopa
  - Tolcapone
L-dopa → Dopamine

3-O-Methyldopa → Tolcapone

Carbidopa → Dopamine

Dihydroxyphenylacetic acid (DOPAC) + H₂O₂

Selegiline

Brain

Striatal neuron

Pergolide and other agonists

D1 and D2 receptors

100%

5%

LAAD Inhibitor

Peripheral tissue

COMTI

Gut

Levodopa

LAAD Inhibitor
Levodopa

- L-dopa or Dihydroxyphenylalanine
- Biosynthetic precursor of dopamine
- Increase dopamine in the brain
- Main treatment used to decrease motor dysfunction
- Absorbed from proximal duodenum
- Protein-restricted diet
- Vit B6 should not be co-administrated with L-dopa
- L-dopa exhibits a large first-pass effect
- Only about 1% reaches brain tissue
Dosage forms of Co-Careldopa

- Levodopa 100 mg Tablet
- Levodopa fort 250 mg Tablet
- Levodopa-C Tablet (100 mg + 10 mg) Sinemet® 110
- Levodopa-C 125 Tablet (100 mg + 25 mg) Sinemet® Plus
- Levodopa-C fort (275)Tablet (250mg + 25mg) Sinemet® 275
Dosage forms of Co-Benzeldopa

- A mixture of Benserazide HCl and levodopa
- Benserazide is a dopa-decarboxylase inhibitor (LAAD inhibitor)
- Levodopa-B 62.5, 125 and 250 (12.5 Benserazide and 50mg levodopa) Tablets
- Madopar® Dispersible Tablets and Capsules
- Madopar® CR (controlled Release)
Mechanism and pharmacologic effect

- L-dopa is taken up by dopaminergic neurons and is converted to dopamine
- Increase dopamine
- As the disease progresses, more dopaminergic neurons are lost and conversion of L-dopa to dopamine decreases
- Wearing off effect
- On-off phenomenon
Adverse effects

- Nausea and vomiting
- Orthostatic hypotension
- Cardiac arrhythmias
- Involuntary movement or dyskinesias
- Psychotic effects
- Sedative effects, agitation, delirium, vivid dreams or nightmare
- Euphoria

Formation of dopamine in peripheral tissues
L-dopa drug interactions

- Anticholinergic drugs may block absorption of L-dopa.
- Drugs that increase gastric emptying may increase L-dopa bioavailability.
- MAO inhibitors may slow metabolism of dopamine and cause a hypertensive crisis in PD patients taking L-dopa.
- Antipsychotics may block dopamine receptors and exacerbate motor dysfunction.
Indications

- Idiopathic parkinson’s disease
- Postencephalic parkinsonism
- Parkinsonian symptoms caused by carbon monoxide poisoning
- Manganese intoxication
- Cerebral arteriosclerosis
Carbidopa

- Is a structural analogue of L-dopa
- Inhibits the conversion of L-dopa to dopamine in peripheral tissue
- It does not cross the blood-brain barrier, so it does not inhibit the formation of dopamine in CNS
- It reduces GI and cardiovascular side effects of L-dopa and enables about 75% reduction in dosage of L-dopa
- L-dopa-carbidopa sustained release combination designed to reduce “wearing off” effect
Amantadine

- It probably increases release of dopamine from nigrostriatal neurons, it may also inhibit reuptake of dopamine by these neurons.
- It is better tolerated than L-dopa or dopamine agonists, but it is also less effective.
- It is used for early or mild parkinsons and an adjunct to L-dopa.
- Its adverse effect: sedation, restlessness, vivid dreams, nausea, dry mouth and hypotension.
- Amantadine Capsule 100mg (Symmetrel®)
It inhibits MAO-B, so prevents oxidation of dopamine to dihydroxyphenylacetic acid (DOPAC) and $\text{H}_2\text{O}_2$

In the presence of iron, $\text{H}_2\text{O}_2$ is converted to hydroxyl and hydroxide radicals.

It inhibits progress of parkinson

Seligiline Tablet 5 mg
Dopamine-producing nerve cell

Chemical that gobbles up dopamine

Dopamine

Eldepryl

Dopamine-receiving nerve cell
Adverse effect

- Selegiline does not inhibit MAO-A, which catalyse degradation of catecholamines.
- It does not cause hypertension when it is administered with sympathomimetics amines or foods contain tyramine, but not in high doses.
- Can cause adverse effect when it is administered with meperidine or SSRI (flutamide).
Indications

- As a single drug for early or mild parkinson disease
- It is used as an adjunct with levodopa-carbidopa for advanced disease
- It reduces the dose of L-dopa and it may improve the wearing off and on-off with levodopa
- It uses as a neuroprotective agent (controversial)
Tolcapone

- It inhibits COMT, which converts levodopa to 3OMD in the gut and liver.
- So it produces a twofold increase oral bioavailability and half-life of levodopa.
- By inhibiting 3OMD formation, it may stabilize dopamine levels in striatum.
Tolcapone (continued)

- Inhibits COMT
- 3OMD competes with L-dopa for transport across the blood-brain barrier and may contribute to the “wearing off” and “on-off” effects seen in patients taking L-dopa
Dopamine receptor agonists

- The drugs work by activating $D_2$ receptors.
- Activation of these receptors inhibits indirect neuronal pathway from striatum to thalamus and increases thalamic stimulation of motor area of cortex.
Bromocriptine and pergolide

- Both ergot alkaloids
- Bromocriptine is a D$_2$ receptor agonist and a D$_1$ receptor antagonist
- Pergolide is a D$_1$ and D$_2$ receptor agonist
- Pergolide is much more potent than bromocriptine, higher affinity to D$_2$ receptors, longer duration of action
- Bromocriptine 2.5 mg Tablet
Both are useful adjuncts to levodopa in patients have advanced parkinson and experience wearing off and on-off

Side effects are nausea (50%), confusion, dyskinesias, sedation, vivid dreams, hallucinations, orthostatic hypotension, dry mouth, decreased prolactin levels
Pramipexole and ropinirole

- They are not ergot alkaloids
- Both act as selective D$_2$ receptor agonists.
- In addition pramipexole activates D$_3$ receptors.
- They can delay the need for levodopa when used in early stages of Parkinson.
- In advanced stages, pramipexole, can reduce the off period and decrease levodopa requirement.
- Pramipexole Tablet 0.18 and 0.7 mg (Sifrol®)
- Ropinirole 0.25, 1 and 5 mg
ACH receptor agonists

- Anticholinergic drugs such as benztropine (Amp 1mg/ml) and trihexyphenedydyl (tablet 2mg) are used.
- They are less effective than dopaminergic drugs.
- They are more effective in reducing tremor than the other symptoms.
- They are useful in treatment of early and advanced parkinson disease, they can reduce parkinsonian symptoms caused by dopamine receptor antagonists eg haloperidol.
New Drugs for Parkinson’s Disease
Treatment Strategies for Parkinson’s Disease

- **Symptomatic**
  - Improve motor symptoms
  - Reduce medication side effects
  - Improve non-motor symptoms
    - Depression
    - Bowel/bladder problems
    - Mentation

- **Neuroprotective**
  - Slow disease progression
  - Reverse brain cell damage
Symptomatic Drugs
MAO-B Inhibitors

- Inhibit degradation of dopamine
- Increase efficacy of levodopa by about 20%
- Reduce “OFF” time
- May increase dyskinesia
- May have neuroprotective properties
MonoAmine Oxidase - B Inhibitors

- Rasagiline
- Zydis-selegiline
Rasagiline (Agilect)

- An irreversible inhibitor of monoamine oxidase type B (MAO-B)
- Selectively inhibits an enzyme that metabolizes dopamine
- Not converted to amphetamine
- Studies underway to examine possible neuroprotection
“Zydis” Selegiline

- A “freeze-dried” tablet of selegiline absorbable through the mucous membrane
- Bypasses the gut and first pass liver metabolism
- Lower doses used: 1.25 mg = 10 mg oral selegiline

Clinical studies:
- Effective as an “add on” to levodopa
- Increased “ON” time by about 1 hour
Orally disintegrating selegiline

Orally disintegrating selegiline

Buccal mucosa

Systemic circulation

Liver

Metabolism

Conventional selegiline

Gut

Liver

Metabolism

Systemic circulation

THE PATCH
Rotigotine CDS (Patch)

- Continuous dopamine agonist delivery
- Absorbable through skin
- Silicone-based Transdermal delivery system
- Replaced every 24 hours
- Side effects similar to other dopamine agonist (nausea, somnolence, etc) and application site reactions
Rotigotine CDS: Results

- Generally well tolerated
- Effective dose
  - Initial therapeutic dose 9 to 13.5 mg/day
  - Dose levels off between 13.5 and 18 mg/day
- Effectiveness similar to other dopamine agonists (Mirapex, Permax, Requip)
A New Target in the Treatment of Parkinson disease:

The Adenosine A2a receptor
Istradefylline

- Selective adenosine $A_{2A}$ receptor antagonist.
- Does not effect other receptors (e.g. dopamine, serotonin, norepinephrine)
- The adenosine $A_{2A}$ receptor in humans
  - Almost exclusively in the striatum
  - Also in the “nucleus accumbens” that appears to play a role in mood.
- In a recent study: effectively improves “off” time
- FDA approval pending
Sarizotan (Anti-dyskinetic)

- Developed by Merke KGaA (Germany)
- Designed as antipsychotic
- Reduced dyskinesia in MPTP-monkey model of Parkinson Disease
- Affects a receptor called $5$-$HT_{1A}$
- Phase III studies are underway to assess the drug’s effect on dyskinesia
Other Receptor Targets of Drugs for PD

NMDA receptor

Ca2+-Calmodulin (CaM)

phosphorylation events

CaM-CaMKII

activated, non-T286 phosphorylated

CaM-CaMKII

T286 autophosphorylated

AMPA receptor
Neuroprotection:

Slowing or Halting the Course of Parkinson’s disease
NET-PD (update)
NEuroprotective Therapy for Parkinson’s Disease
The Screening Process

- Four candidate drugs were screened for 12 mos.
  - Minocycline (200 mg/day)
  - Creatine (10 g/day)
  - GPI-1485 (1000 mg/day)
  - Co enzyme Q (2400 mg/day)

- Subjects were not requiring treatment at entry

- PD course was charted using a standard clinical rating scale (UPDRS)

- UPDRS scores of treatment groups were compared to placebo groups

- The study design:
  - Was not powered to measure efficacy ---
  - But rather to detect a trend toward slower progression compared to the placebo group
Preliminary Results of NET-PD Study

- All four compounds were well tolerated
- UPDRS scores appeared slower in all four treatment groups compared to placebo
- Re-analysis using a placebo from a recent study indicated that Creatine appeared more robust than the other three compounds
- The next step is a long term efficacy study
Creatine

- Dietary supplement
- Important role in mitochondrial energy production
- Absorbed orally
- Appears safe and well tolerated
- Neuroprotective in laboratory models of Parkinson disease
Long-term Study

- Multiple study sites
- Subjects will be in the early stage of PD, but receiving medication (e.g. levodopa and/or dopamine agonists).
  - PD no more than 3 years
  - Stable, without fluctuations or dyskinesia
- Large # of subjects (about 1000)
- Measures of progression will include:
  - Onset of postural instability
  - Onset of freezing of gait
  - Onset of mental problems
  - Onset of motor fluctuations
Conclusions

- New Drugs will soon be available to improve the motor features of PD
- Drugs are being studied that target nerve cell receptors other than dopamine
- Drugs that improve “non-motor” symptoms of PD are needed
- The search for drugs that could slow or halt the progression of PD is underway
Huntington’s disease

- Characterized by loss of GABAergic medium spiny projection neurons in the striatum
- Caused by glutamate-induced neurotoxicity (?)
- Loss of GABAergic neurons that project of GP leads to disinhibition of thalamic nuclei and increase output to motor area of the cortex
- Symptoms consistent with excess dopaminergic activity
Huntington’s disease

- D2 receptor antagonist such as haloperidol and chlorpromazine have some effect at controlling the excess movement and some aspects of the psychiatric dysfunction.
- Diazepam potentiates GABA and may reduce excess movement but only in the early stages of the disease.
- Depression and impulsive behaviours may respond to antidepressant or propranolol (β-adrenergic antagonist).
Relatives of Parkinson's disease patients were 37 percent more likely to show thinking deficits or dementia than were relatives of unaffected subjects, the report indicates.
Scientists Find Nicotine May Ease Symptoms of Parkinson's (10/24/2007)

The researchers found that the nicotine-treated monkeys had up to 50 percent fewer episodes of dyskinesias, compared with monkeys that had not received nicotine before being given levodopa.
Over-the-Counter Pain Medications May Reduce Risk of Parkinson’s Disease (10/31/2007)

Our findings suggest NSAIDs are protective against Parkinson’s disease, with a particularly strong protective effect among regular users of non-aspirin NSAIDs, especially those who reported two or more years of use,”
We found that, indeed, relatives of patients with Parkinson's disease are at increased risk for anxiety and depressive disorders, which suggests a genetic or other relationship between those disorders and Parkinson's disease.
There you have it!
Increase availability of dopamine

Reduce acetylcholine activity

Slow the loss of dopamine