Parkinson’s Disease and Treatment

GPe – Globus pallidus externus
GPI – Globus pallidus internus
PUT – Putamen
SN – Substantia nigra
STN – Nucleus subthalamicus
THA – Thalamus
Mesencephalon
Introduction

The shaking palsy (Parkinson - 1817)
A prevalent, progressive neurodegenerative disease
Biochemical lesion - neurodegeneration
No cure, no means to prevent the degeneration of neurons
Treatment based on knowledge of biochemical lesion
Parkinson’s Disease

PD affects over 1 million Americans.

It is second only to Alzheimer’s disease as the most common degenerative disease of neurons.

Symptoms generally appear in middle age and continue becoming more and more severe with age.

There is no cure available.

Drug therapy can maintain functional mobility for years (prolongs/improves quality of life).
Symptoms

Tremor
bradykinesia
Rigidity
Postural effect
Dementia
Causes

Genetics?
Environment?
Drug induced
Environmental toxins?
Parkinsonism and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
Substantia nigra

Cut section of the midbrain where a portion of the substantia nigra is visible.

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease.
Dopamine restoration in brain

- Need to restore dopamine in brain
- Blood brain barrier for dopamine

- Levodopa as a precursor to dopamine
- Decarboxylation to dopamine
- Use of Levodopa (L-dopa)
- Aromatic L-Amino Acid decarboxylase
Dopamine restoration in brain

1. Blood-brain barrier
2. Levodopa
3. Terminal of a dopaminergic neuron
4. Dopamine (DA)
5. GABAergic neuron

Levodopa is transported across the blood-brain barrier, converted to dopamine in the terminal of the dopaminergic neuron, and then binds to the dopamine receptor.
Central availability

(Data in the figure are extrapolated from Nutt JG, Felmance JH. Pharmacokinetics of levodopa. Clin Pharmacol 7:35, 1984.)
Preservation of L-DOPA and striatal dopamine

COMT: Catechol-O-methyltransferase
AADC: Aromatic L-amino acid decarboxylase
DOPAC: 3,4-dihydroxyphenylacetic acid
3MT: 3-methoxyltyramine
3-O-MD: 3-O-methyl DOPA
DA: Dopamine
MAO-B: Monoamine oxidase-B
Side effects

Peripheral decarboxylation produces peripheral side-effects

Generally dose-dependent and reversible

Gastrointestinal (Caution: Don't use phenothiazines for nausea)

Cardiac irregularities (β-adrenergic receptors)

Behavioral disturbances (role of dopamine)

Special care: cardiac arrhythmias, major psychoses

Abnormal involuntary movements - a serious side effect, no tolerance, may limit the dose
L-Dopa/Carbidopa therapy

Generally a combination of levodopa and carbidopa given

Gradual increase in dose

Careful Individual titration needed

Complications of dyskinesias

Limitations with respect to long-term treatment

Not a cure
Other drugs

Dopaminergic agonists - pramipexole, ropinirole

Anticholinergic drugs - benztropine, trihexyphenidyl

A  Normal

B  Parkinson’s Disease
Other drugs

Selegiline & Rasagiline:
- Selective inhibition of MAO-B
- MAO-B present predominantly in the striatum
- Inhibition of the breakdown of dopamine by MAO-B

Entacapone: catechol-o-methyl transferase inhibitors - inhibition of dopamine degradation
Other drugs

Amantadine: blockade of NMDA receptors - treatment of levodopa-induced dyskinesias
Effectiveness of the treatment

- Effective relief from symptom for several years
- Implications of protection from progressive neurodegeneration
A possibility to prevent cell death?

Implications of protection from neurodegeneration
MPTP Induced Parkinsonism

A major advance in 1979 - the case of a young man
Link with MPTP
The "Frozen Addict" patients
Insights from MPTP induced Parkinsonism

- Parallels in symptoms, pathology, treatment, complications
- Dopamine depletion without symptoms
- Animal models using MPTP
- Environmental toxins and Parkinson's Disease
- Rotenone and Parkinson's disease
The objectives of the lecture on Parkinson’s Disease (PD) are to understand:

- The pathology underlying PD
- The role of dopaminergic neurotransmission in PD
- Drug treatments available to reduce the symptoms of PD, including levodopa-carbidopa therapy and other drugs that may be useful
- Enzymatic pathways involved in Dopamine synthesis and its breakdown.
- MPTP induced Parkinsonism and the role of environmental toxins in PD