Basal ganglia

Nuclei in white matter of brain . They constitute the extrapyramidal system . Include : caudate , putamen and globus pallidus nuclei,

and nuclei in midbrain (substantia nigra, subthalamic nuclei)

Caudate + putamen = neostriatum

Caudate + putamen + globus pallidus = corpus striatum

- Extrapyramidal system plays an important role in motor control .

Disorders of the basal ganglia

Hyperkinesia

Chorea (lesion in caudate)

Athetosis (lesion in putamen)

Ballism (lesion of subthalamic nuclei)

hypokinesia

Parkinsonism (lesion of substantia nigra)

Parkinson’s disease (paralysis agitans , shaking palsy)

Parkinson's disease and the eponymous syndrome are caused by degeneration of dopaminergic neurons in the nigrostriatal pathways .

- Occurs in 10% of people commonly in the elderly .

Major signs

- Poverty of movement (bradykinesia)
- Muscle stiffness (rigidity)
- Tremors at rest
- Impaired postural balance (abnormal gait and falling)
- Depressed mood, saliva drooling, dementia , sweating)

The disease is progressive if not treated.

Aetiology :

Parkinsonism

Idiopathic
(cause unknown)
(Parkinson’s disease)

iatrogenic
(drug-induced)

Idiopathic (cause unknown)

- Irreversible
- Genetic factor
- Neurotoxin-induced (endogenous or environmental)

MPTP----MAO type B------→MPP + .

free radical

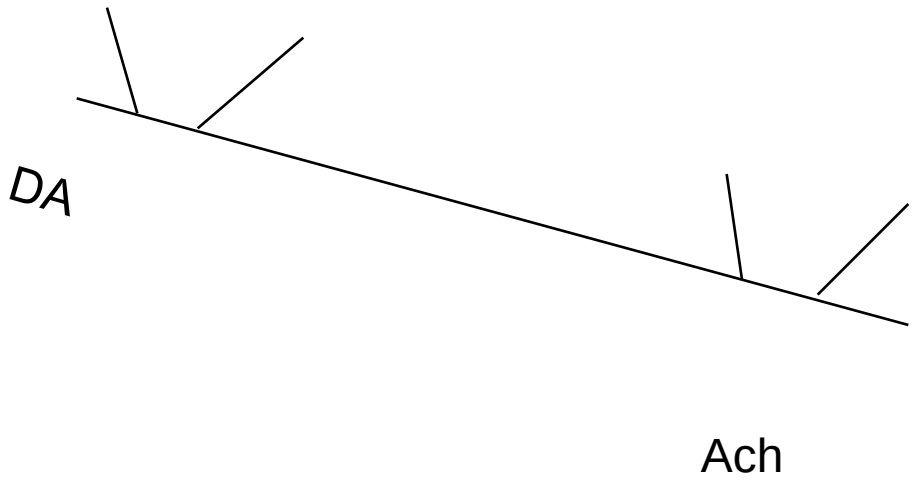
- Poisoning →(CO , Manganese , methanol)
- Viral
- Post-encephalitic
- Vascular (arteriosclerosis)
- Traumatic

Iatrogenic (drug-induced)

- Reversible
- Dopamine antagonists e.g. chlorpromazine
- Dopamine depleters e.g. reserpine
- α-methyl-dopa

Treatment of Parkinsonism

- Parkinsonism →imbalance between DA and Ach in striatum .



A. Dopaminergic drugs :-

- Dopamine does not cross B.B.B.
- Use dopamine precursor →L-dopa (crosses B.B.B.)
- Dopamine D2 agonists
- Dopamine releasers
- MAO type B inhibitors .
- COMT inhibitors

B. Centrally acting muscarinic antagonists

C. Transplantation of dopaminergic neurons

Levodopa (L-dopa)

M.O.A. :Restores striatal DA level

L-dopa---dopa decarboxylase---→Dopamine

- Used in combinatin with peripheral dopa decarboxylase inhibitors (e.g. carbidopa or benserazide →do not cross BBB)

- Combination →decrease dose of L-dopa → decrease side effects.

Major adverse effects of L-dopa

- Choreiform or dystonic movements
- (chorea →increased dopamine and decreased GABA in basal ganglia)
- Nausea and vomiting (reduced by a peripheral dopamine antagonist e.g. domperidone)
- Anorexia
- Cardiac dysrhythmias
- Hypotension
- Psychosis
- insomnia

Long term toxicity of L-dopa

1. Loss of effect of drug after 5 years
2. End of dose effect (duration becomes shorter)
3. On-off effect (mobility → dyskinesia)

   (controlled by I.V. dopa,

   or S.C. apomorphine,

   or oral bromocriptine)

Contraindications of L-dopa

1. Concurrent use of MAOI (type B) which produce serious interactions with tyramine-containing food .

   Not contraindicated with selegiline (MAO type B inhibitor) as no serious interactions with tyramine-containing food .

1. Patients with cardiac disorders and psychosis
2. Abrupt drug withdrawal (muscular rigidity, increased body temp., mental changes)

- **Dopamine Agonists**
- • Mirapex® - pramipexole
- • Requip® - ropinirole
- • Permax® - pergolide
- • Parlodel® - bromocriptine

Dopamine receptor agonists :

1. Bromocriptine

- Given with dopamine in the late stages
- Same side effects of L-dopa but more severe .
- Useful in treatment of increased prolactin secretion

:. Useful in treatment of infertility .

- Useful in treatment of acromegaly (due to increased growth hormone release) .

2. Apomorphine: dopamine agonist (sublingual)

Drugs causing dopamine release :

e.g. Amantadine :

Antiviral agent (against influenza)

MAO inhibitors :

e.g. Selegiline

Increase dopamine by preventing its inactivation by MAO enzyme .

- Also useful in Alzheimer's disease (decreased acetylcholine in brain) .

COMT Inhibitors

- **Tolcapone (Tasmar®)**
- • Catechol-O-methyltransferase inhibitor that will increase response to levodopa
- • Side effects
- – Nausea, vomiting, diarrhea, confusion,
- dyskinesias, orthostasis
- – Fatal liver disease
- • Contraindicated in patients with underlying
- liver disease

COMT Inhibitors

- **Entacapone (Comtan®)**
- • Catechol-O-methyltransferase inhibitor
- • Adjunct to levodopa/carbidopa in patients with end-of-dose “wearing-off”
- • Adverse Effects
- – hypotension, syncope, diarrhea, hallucinations, dyskinesias, rhabdomyolysis, hyperpyrexia, confusion
- • Use caution in liver disease

Anticholinergic drugs (atropine-like drugs)

e.g. Benzhexol :improves tremors

side effects :

- Dry mouth &skin
- Urinary retention
- Constipation
- Decreased memory .

- **Anticholinergics**
- • All agents are equally efficacious
- • benztropine (Cogentin®)
- • trihexyphenidyl (Artane®)
- • diphenhydramine (Benadryl®)
- • procyclidine (Kemadrin®)
- • biperiden (Akineton®)
- • orphenadrine (Disipal®)

Neurotransmitters in the basal ganglia

- Dopamine → in nigrostriatal pathways
- GABA → From neostriatum to substantia nigra and globus pallidus
- ACh →interneurons in neostriatum .
- ↓DA and ↑ACh →Parkinson's disease
- ↑DA and ↓GABA → Chorea

Proper function of ganglia requires a balance of dopamine, Ach and GABA .