Pathophysiology of Parkinson’s Disease and Motor Complication

S. Muchimapura
Department of Physiology  Faculty of Medicine
Khonkaen University

NNA January 19, 2005
An overview

- Parkinson's disease (PD) is a progressive neurodegenerative disorder.
- “James Parkinson”
- PD has the cardinal features of bradykinesia, muscle rigidity, tremor at rest, and postural instability.
- Parkinson's disease affects mainly the elderly - about 1% of the population over 65 is affected.
- **Internationally**: Overall incidence of PD is about 10-20 cases per 100,000 population per year.
An overview

- African-Americans and Asians less likely than Caucasians to develop Parkinson’s
- Everyone loses some dopamine-producing neurons as a normal part of aging.
- People with Parkinson's disease lose at least 60 percent of neurons in the substantia nigra, pars compacta.
- Other neural systems are also affected; noradrenergic, serotonergic, and cholinergic systems that project to the cortex and limbic structures.
Causes of Parkinson’s Disease

- **Normal Ageing** - very unlikely
- **Genetic** - evidence for a susceptibility role and in very rare cases it is purely genetic.
- **Environmental** - certain drugs and neurotoxins cause PD
- **Genetic susceptibility to environmental factors**
- **Metabolic dysfunction** - Oxidative stress
The UK Parkinson's Disease Society Brain

Bank criteria for clinical diagnosis include the following three:

1. Bradykinesia plus one of rigidity, tremor, or postural instability.

2. At least three of rest tremor, progressive symptoms, unilateral onset, early response to levodopa, levodopa-induced dyskinesia.

3. No identifiable cause for the parkinsonism.
Characteristic Problems

- Micrographia - small handwriting
- Hypomimia - decreased facial animation
- Hypophonia - soft speech
- Dysarthria - unclear pronunciation
- Dyspnea - labored breathing
- Festination - Shuffling gait
Pathology Parkinson’s disease

- Lewy body is the pathological characteristic of Parkinson’s disease.
- Lewy body is an eosinophilic intracytoplasmic inclusion. Lewy bodies can be seen in the pigmented brain stem, throughout the brain and cerebral cortex.
- Lewy bodies can be detected in post-mortem brain tissue by using antibodies to ubiquitin and antibodies to alpha-synuclein.
Lewy body: Neurofilaments + ubiquitin + Alpha-Synuclein

Abnormal phosphorelation occurs to neuronal cytoskeletal.
**Left:** Midbrain section showing loss of pigmented cells of the substantia nigra in Parkinson's disease.

**Right:** Midbrain section showing normal substantia nigra. From: *CNS Pathology.*
Left: Histology of Parkinson's disease showing loss of pigmented neurons in substantia nigra.
Right: Histology of normal substantia nigra showing many pigmented neurons. From: CNS Pathology
In Parkinson's disease there is a decreased level of dopamine in certain areas of the brain. Figure is a PET study showing the difference in F-DOPA levels between controls and Parkinson's Disease.
Neurophysiology
Parkinson's disease

• The symptoms in Parkinson's disease are generated from the complexity of the physiological mechanisms.

• In general, the striatum controls the activity of basal ganglia output neurones via two major routes: the direct pathway and the indirect pathway.

• Subsequently from the loss of striatal dopamine that occurs in Parkinson's disease, these routes fail.
Motor complication in PD

1. Negative motor activities:
   - Akinesia
   - Impaired postural balance

2. Positive motor activities:
   - Rigidity
   - Rest tremor
The Motor System

- Muscle tone
- Posture and equilibrium
- Movement
PLAN, PROGRAM

IDEA

Association Cortex

BASAL GANGLIA

VL THAL

MOTOR CORTEX

Intermediate cerebellum

MOVE

Association cortex, Subcortical areas, Basal ganglia, Lateral Cerebellum

SOMATO-SENSORY
C-shaped configuration of caudate nucleus and disk shape of the putamen
Components of the Basal Ganglia

Input nuclei (striatum)
1. Caudate nucleus
2. Putamen
3. Nucleus accumbens

Output nuclei
1. Substantia nigra pars reticulata
2. Globus pallidus-internal segment
3. Ventral pallidum

Intrinsic nuclei
1. Globus pallidus-external segment
2. Subthalamic nucleus
3. Substantia nigra pars compacta
4. Ventral tegmental area
Functions of the Basal Ganglia

1. Motor planning and programming **Strategies**
   - Control organized or skilled movement
2. Cognitive process
   - Planning for order of movements
3. Control of speed or magnitude of movement
4. Initiation of movement

"control axial and proximal musculature"
Dopamine receptors

a) D1 (D1, D5)
   • Activation of D1 receptors $\rightarrow$ excitatory response
   • Neurons containing D1 receptors project from the striatum (caudate and putamen) to globus pallidus internus (GPI), which are considered as part of the direct pathway.

b) D2 (D2, D3, D4).
   • Activation of D2 receptors $\rightarrow$ inhibitory response.
   • Neurons containing D2 receptors are considered part of the indirect pathway.
   • Neurons containing the D2 receptors project from the striatum to globus pallidus externus (GPE), which then projects to GPI via the subthalamic nucleus.
Direct Pathway

• This is the simplest pathway through basal ganglia.

• Striatopallidal neurones induce an inhibition via g-aminobutyric acid and substance P upon internal pallidal neurones (GPi) which are themselves inhibitory to target neurones.

• This leads to disinhibition of the motor thalamus and to an increase in the firing rate of its cells.

• The proposed effect of activation of the 'direct' pathway is to support or facilitate ongoing movements.
Indirect Pathway

via the subthalamic nucleus (STN).

• Efferents from the striatum terminate in the external globus pallidus (GPe). Activation of these efferents releases g-aminobutyric acid and enkephalin, which inhibit the external pallidal neurons.

• The GPe themselves have an inhibitory projection to the subthalamic neucleus (STN).

• The STN is therefore disinhibited and its cells increase firing that leads to activation of internal pallidal (GPi) and nigral (SNr) neurones.
Indirect Pathway
via the subthalamic nucleus (STN).

- The output from GPi to thalamus is inhibitory, reducing the excitatory thalamic input to supplementary motor areas.

- The indirect pathway is thought to inhibit unwanted movement.
Direct Pathway

• In Parkinson's disease, the depletion of dopamine (acting mainly through D1 receptors - excitatory) from the nigrostriatal projection zones in the striatum, results in the direct pathway being underactive.

• This leads to decreased firing of thalamic neurones and hence inhibition of initiation of movement.
Indirect Pathway

• In PD, depletion of dopamine (acting through D2 receptors - inhibitory) from the nigrostriatal projections in the striatum, results in the indirect pathway being overactive.

• The combined hyperinhibitory outflow from GPi may account for the negative symptoms of PD (rigidity and bradykinesia).

• In addition, tremor activity is generated in the ventrolateral (VL) nucleus of the thalamus, thus this region may be the site to be considered to treat parkinsonian tremor.
Glutamate overactivity
Bradykinesia

- Bradykinesia: akinesia, hypokinesia
- Bradykinesia describes the slowness of a performed movement
- Akinesia refers to a poverty of spontaneous movement (e.g. in facial expression) or associated movement (e.g. arm swing during walking).
- Akinesia: freezing and the prolonged time it takes to initiate a movement.
- Hypokinesia refers to being slow and the movements are also smaller than desired, as in the micrographia of patients' handwriting.
Bradykinesia

- Premotor area: motor programs
- Sensorimotor cortex
- Flexor-extensor muscle

- The majority of the basal ganglia output, particularly that in the `motor loop' projects back to the cortex via the thalamus.

- A direct relationship between the level of discharge in the output nuclei and the amount of observable movement, a high output causing hypokinesia and a low output causing hyperkinesia (Wichmann and De Long, 1996).
• There are two different functional zones within the globus pallidus internus (Krack et al., 1998)

• Stimulation in the ventral zone
  – ↓ drug-induced dyskinesias and improved rigidity

• Stimulation at a more dorsal site near the border of the globus pallidus internus and the globus pallidus externus
  – : improved OFF-drug bradykinesia but could also induce dyskinesias in some patients.
Postural fixation, equilibrium and righting

- Adjustment of the center of gravity by adjusting flexor-extensor muscular tone of axial and proximal musculature
  - Spinal segmental reflex (1\textdegree, 2\textdegree muscle spindle)
  - Supraspinal reflex (vestibular apparatus, proprioceptors, visual input)

- PD: abnormality of supraspinal reflex

\begin{tikzpicture}

\node (n1) at (0,0) {Normal sensory inputs};
\node (n2) at (2,0) {Vestibular nucleus};
\node (n3) at (4,0) {Thalamus};
\node (n4) at (6,0) {Pulldum Striatum};
\node (n5) at (-2,-2) {Abnormal output};

\draw[->] (n1) -- (n2);
\draw[->] (n2) -- (n3);
\draw[->] (n3) -- (n4);
\draw[->] (n4) -- (n5);
\end{tikzpicture}
Rigidity

↑ muscle tone both agonist and antagonist

↓ muscle stiffness

• Abnormality of tonic stretch reflex (\(2^\circ\) muscle spindle) + long latency stretch reflex (descending impulse from cerebral cortex)

• Extrapyramidal system = cogwheel rigidity
Rigidity

Premotor area: motor programs

Sensorimotor cortex

↑ Flexor muscle tone

• ↑ Activity tonic stretch reflex (2° muscle spindle)
• ↑ Activity long latency stretch reflex (descending impulse from cerebral cortex)

• Abnormal of sensorimotor cortex and basal ganglia circuit → ↑ flexor muscle tone
Tremor

• 4-6 Hz resting tremor alternative action between agonist and antagonist.

Ventralis intermedius nucleus of the thalamus (central oscillator)
References

• A. Berardelli, J. C. Rothwell, P. D. Thompson and M. Hallett Pathophysiology of bradykinesia in Parkinson's disease Brain, Vol. 124, No. 11, 2131-2146, November 2001
http://brain.oupjournals.org/cgi/content/full/124/11/2131
• http://www.macalester.edu/~psych/whathap/UBNRPParkinsons/webpage.html
• http://www.gwc.maricopa.edu/class/bio201/parkn/jcadis51.htm
• http://www.wemove.org/par_mss2.html Abraham N. Lieberman, M.D., Medical Director, National Parkinson Foundation
• “Early Parkinson’s Disease: Dopamine Agonists Have Increasingly Important Role in Symptom Management.” Drug Ther Perspect 2001;17(17):5-9.
• Faulkner, Thomas P. “Parkinson’s Disease,” 7 December 1999.
Thank You
For Your
Attention