Parkinson Disease
An Essay

On the Shaking Palsy.

By James Parkinson,
Member of the Royal College of Surgeons.

London: Printed by Whittingham and Rowland,
Grosvenor Street,
For Sherwood, Neely, and Jones,
Paternoster Row.

1817.
Cardinal symptoms of PD:
bradykinesia, hypo- / akinesia, muscle stiffness, resting tremor (asymmetric onset), postural instability, speech and writing disorders, forward bent posture, small gait and freezing (sudden stops in gait)

Non-motor symptoms:
hypotension, constipation, bladder dysfunction and thermoregulation along with sleep disorders, fatigue and weight loss

Depression, anxiety, cognitive deficits
A. Normal

B. Parkinson's Disease

Nigrostriatal pathway

C. Lewy Body

Synuclein

Ubiquitin
Parkinson’s disease progression

Braak stages 1 and 2
Autonomic and olfactory disturbances

Braak stages 3 and 4
Sleep and motor disturbances

Braak stages 5 and 6
Emotional and cognitive disturbances

Via olfactory bulb
Premotor symptoms
Via vagus nerve
Motor symptoms

Alfa synuclein ad Lewy bodies

Brainstem Lewy body
Cortical Lewy body
Difference in fluoro-dopa levels between healthy subjects and parkinsonian
Figura 27.3. Rappresentazione classica dei nuclei della base in condizioni fisiologiche (A), e in presenza di disordini del movimento quali la malattia di Parkinson (B) e la malattia di Huntington (C). Per le abbreviazioni vedere il testo. La linea tratteggiata indica le popolazioni neuronali che vanno incontro a degenerazione nelle due patologie. Obeso et al., Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci, 23, S8, 2000.
Environmental Factors
- Rotenone
- Paraquat
- MPTP

Oxidative stress
ROS production
excitotoxicity

Mitochondrial dysfunction
mtDNA mutations
Misfolded proteins

Genetic mutations
- α-Synuclein
- LRRK2
- DJ-1
- PINK1
- Parkin

Death of DA Neurons in SNpc

PD
Genetic mechanisms involved in Parkinson's disease

**α-synuclein** in the locus 4q21-23, (onset around 45 years and with rapid symptoms)

**DJ-1**, in the 1p36 locus, causes modifications of α-synuclein

**parkin**, in the locus 6q25.2-27, (juvenile forms, with onset around the age of 32, characterized by the absence of Lewy bodies in the brain) is a **ubiquitin ligase**

**leucine-rich repeat kinase 2 (LRRK2)**, (interacts with the terminal c of parkin), the mutated LRRK2 causes apoptosis. Present in cytoplasm and mitochondria

**hydrolase of C-terminal ubiquitin L-1 (UHC-L1)**, in the 4p-14 locus (proteins destined to be degraded by the ubiquitin system are previously labeled with poly-ubiquitin chains and subsequently degraded by the proteasome)

**PINK 1** (PTEN-induced kinase 1) located in the mitochondria
"Misfolding" proteine

Ripiegamento corretto
Mantengono parziale denaturazione
Stabilizzano proteine danneggiate (stress chimici o fisico)
Facilitano degradazione
Alpha Synuclein

N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-complex
Alfa-synuclein

1. $\alpha$-Synuclein protofibrils (oligomers)
2. Interaction with potential neurotoxic proteins
3. Dopamine neuron cell death
   - Motor impairment
4. Chaperone depletion
5. Lewy bodies

Chaperone

Non-toxic $\alpha$-synuclein conformations
Oxidative Stress

ROS

\[ \cdot O_2^- \quad \cdot OH \quad H_2O_2 \]

ATTACCANO GRUPPI SH (PROTEICI)
IMPEDISCONO GENERAZIONE ATP DA MITOCONDRI
GENERANO AGENTI OSSIDANTI H_2O_2
INATTIVANO ENZIMI
ATTACCANO DNA (SINTESI ERRATA)
ATTACCANO FOSFOLIPIDI
Le difese contro il danno ossidativo

Una serie di difese previene o ripara il danno molecolare causato dai radicali liberi, ma la loro azione è nell’insieme imperfetta. Sembra che alcune di queste difese con il passare del tempo diventino meno efficaci.

<table>
<thead>
<tr>
<th>CLASSE</th>
<th>MOLECOLA</th>
<th>ATTIVITÀ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENZIMI</td>
<td>Superossido-dismutasi</td>
<td>Trasformano il radicale superossido in perossido di idrogeno</td>
</tr>
<tr>
<td>ENZIMI</td>
<td>Glutatione, perossidasi e catalasi</td>
<td>Convertono il perossido di idrogeno in acqua e ossigeno molecolare</td>
</tr>
<tr>
<td>ANTISSIDANTI</td>
<td>Vitamina E e beta carotene</td>
<td>Reagiscono con i radicali liberi, impedendo loro di attaccare le strutture cellulari; sono liposolubili e quindi riescono a proteggere le membrane</td>
</tr>
<tr>
<td>ALTRE SOSTANZE</td>
<td>Acido urico e vitamina C</td>
<td>Reagiscono con i radicali liberi del citoplasma</td>
</tr>
<tr>
<td></td>
<td>Chelanti dei metalli</td>
<td>Impediscono al ferro, al rame e ad altri metalli di transizione di catalizzare le reazioni ossidative</td>
</tr>
</tbody>
</table>
Enzymes

- **SUPEROXIDE DISMUTASE**
  \[ \text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \]

- **CATALASE**
  \[ 2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2 \]

- **PEROXIDASE**
  \[ \text{H}_2\text{O}_2 + \text{R(OH)}_2 \rightarrow \text{RO}_2 + 2\text{H}_2\text{O} \]

- **GLUTATIONE PEROXIDASE**
  \[ 2\text{GS} + \text{H}_2\text{O}_2 \rightarrow \text{GS}-\text{SG} + 2\text{H}_2\text{O} \]
  \[ \text{ROOH} + 2\text{GS} \rightarrow \text{ROH} + \text{GS}-\text{SG} + \text{H}_2\text{O} \]
Excitotoxicity and oxidative stress

- Excitatory amino acids (EAA, e.g. glutamate) can cause neuronal death.
- Excitotoxicity is associated mainly with activation of NMDA-receptors, but other types of EAA receptors also contribute.
- Excitotoxicity results from a sustained rise in intracellular Ca\(^{2+}\) concentration (Ca\(^{2+}\) overload).
- Excitotoxicity can occur under pathological conditions (e.g. cerebral ischaemia, epilepsy) in which excessive glutamate release occurs. It can also occur when chemicals such as kainic acid are administered.
- Raised intracellular Ca\(^{2+}\) causes cell death by various mechanisms, including activation of proteases, formation of free radicals, and lipid peroxidation. Formation of nitric oxide and arachidonic acid are also involved.
- Various mechanisms act normally to protect neurons against excitotoxicity, the main ones being Ca\(^{2+}\) transport systems, mitochondrial function and the production of free radical scavengers.
- Oxidative stress refers to conditions (e.g. hypoxia) in which the protective mechanisms are compromised, reactive oxygen species (ROS) accumulate and neurons become more susceptible to excitotoxic damage.
- Excitotoxicity caused by environmental chemicals may contribute to some neurodegenerative disorders.
- Measures designed to reduce excitotoxicity include the use of glutamate antagonists, calcium channel blocking drugs (calcium antagonists) and free radical scavengers; none is yet proven for clinical use.
Neuroinflammation
Glucocerebrosidase deficiency
Mutation in glucocerebrosidase (GBA) gene and ASN aggregation

(A) Normally functioning lysosome, wild-type glucocerebrosidase might interact with α-synuclein, facilitating the lysosomal component of α-synuclein degradation. (B) In most cases, when glucocerebrosidase is mutated, α-synuclein remains in the monomeric form and other processes are active in its degradation. (C) In some patients, glucocerebrosidase is mutated and the cell is unable to degrade α-synuclein. Lysosomal function is compromised and increased oligomeric forms of α-synuclein lead to neuronal cell death and the development of parkinsonism.
Normal Functioning Lysosome

WT GCase
SNCA

Autophagy
Degraded SNCA

Lysosome with mutant GBA

SNCA aggregates

ER
Golgi
Nucleus
GCase

A
B
C
D
E
Mutations in the glucosylceramidase beta (GBA) gene are associated with neurodegenerative diseases marked by protein aggregation

GBA encodes the lysosomal enzyme glucocerebrosidase, which breaks down glucosylceramide

The link between GBA mutations and protein aggregation is that lysosomal accumulation of glucosylceramide causes impaired autophagy

Changes in the turnover and abundance of proteins is associated with extracellular vesicles (EVs), which are vehicles for the spread of protein aggregates in neurodegenerative disease

Gba1b mutants had six times as many EVs as controls

EV abundance contributed to the accumulation of protein aggregates

Glucocerebrosidase deficiency causes pathogenic changes in EV metabolism and may promote the spread of protein aggregates through extracellular vesicles
Parkinson's disease: from dopamine precursors to new generations of drugs

WR Gowers, 1888
Pharmacological treatments
- L-DOPA (precursor of dopamine)
- Direct DA agonists with long half-lives
- COMT or MAO inhibitors
- Glutamate antagonists
  - Anticholinergic

Surgical treatments
- Pallidotomy
- Deep brain stimulation
- Stem cell transplantation
<table>
<thead>
<tr>
<th>FARMACI O CLASSE DI FARMACI</th>
<th>MECCANISMO D'AZIONE</th>
<th>EFFETTI COLLATERALI</th>
<th>FARMACI SPECIFICI</th>
<th>DOSE GIORNALIERA TOTALE MEDIA</th>
<th>FREQUENZA MEDIA DI SOMMINISTRAZIONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA</td>
<td>Metabolizzata in dopamina dall'enzima dopa-decarbossilasi</td>
<td>Acuti: Nausea, ipotensione, allucinazioni e psicosi. Cronici: fluttuazioni motorie, movimenti discinetici</td>
<td>L-DOPA/ carbidopa (250/25) L-DOPA/benserazide</td>
<td>400/40-800/80 mg 400/100-800/200 mg</td>
<td>3-4 volte al giorno 3-4 volte al giorno</td>
</tr>
<tr>
<td>Agonisti dopaminergici</td>
<td>Stimolazione diretta dei recettori dopaminergici</td>
<td>Nausea, ipotensione, allucinazioni e psicosi, edema periferico, fibrosipolmonare (per i derivati dell'ergot), improvvisi colpi di sonno</td>
<td>Derivati ergolinici* Bromocriptina Cabergolina</td>
<td>15-30 mg 2-6 mg 60-120 mg 1.5-4.5 mg 1.5-3 mg 12-84 mg 150-250 mg 1.5-4.5 mg 3-9 mg 6-8 mg</td>
<td>2-3 volte al giorno 1 volta al giorno 2 volte al giorno 2 volte al giorno 3 volte al giorno Infusione continua per 12 ore 3 volte al giorno 3 volte al giorno 3 volte al giorno Rilascio transdermico</td>
</tr>
<tr>
<td>Anticolinergici</td>
<td>Antagonismo dei recettori colinergici</td>
<td>Secchezza delle fauci e oculari, ritenzione urinaria, peggioreamento del glaucoma e deficit cognitivi</td>
<td>Biperidene Bornaprina Metixene Orfenadrina Triésiflenilide</td>
<td>1-6 mg 6-12 mg 20-60 mg 200-400 mg 6-10 mg</td>
<td>3 volte al giorno 3 volte al giorno 3 volte al giorno 3 volte al giorno 3 volte al giorno</td>
</tr>
<tr>
<td>Amantadina</td>
<td>Antagonismo dei recettori NMDA nicotinici, promozione del rilascio di dopamina</td>
<td>Disfunzioni cognitive, edema periferico e eruzioni cutanee</td>
<td>Amantadina</td>
<td>50-200 mg</td>
<td>2 volte al giorno</td>
</tr>
<tr>
<td>Inibitori delle MAO</td>
<td>Inibizione delle MAO-B e riduzione del metabolismo della dopamina</td>
<td>Disordini del sonno e deficit cognitivi, nausea, vertigini</td>
<td>Selégilina Rasagilina</td>
<td>5-10 mg 1-4 mg</td>
<td>2 volte al giorno 2 volte al giorno</td>
</tr>
<tr>
<td>Inibitori delle COMT</td>
<td>Inibizione delle COMT e aumento dei livelli della L-DOPA</td>
<td>Esacerbazione degli effetti collaterali della L-DOPA, diarrea</td>
<td>Entacapone</td>
<td>200 mg per ogni dose di L-DOPA</td>
<td>Si associa ad ogni dose di L-DOPA</td>
</tr>
</tbody>
</table>
Levodopa
Marketed preparations:
- **L-dopa + benzerazide:**
  - Madopar 125 mg dispersible tablets (Roche)
  - Madopar 125 mg tablets (Roche)
  - Madopar 250 mg divisible tablets (Roche)
  - Madopar HBS 125 mg tablets (Roche) – controlled-release preparation

  **Posology:** The average efficacious dose is 600–800 mg/day, but should be established on an individual basis. The daily dose of Madopar HBS must be about 50% higher than that of the non-delayed formulations.

- **L-dopa + carbidopa:**
  - Sinemet 25/100 mg tablets (Bristol-Myers Squibb)
  - Sinemet 25/250 mg tablets (Bristol-Myers Squibb)
  - Sinemet CR 25/100 mg tablets (Bristol-Myers Squibb) – controlled-release preparation
  - Sinemet CR 50/200 mg tablets (Bristol-Myers Squibb) – controlled-release preparation

  **Posology:** The average efficacious dose is 200–600 mg/day, and the maximum dose 2000 mg/day. The average efficacious dose of Sinemet CR is 400–1000 mg/day.

- **L-dopa methyl hydrochloride:**
  - Levomet bottles of powder + solvent: 1 ml of reconstituted solution = 251.2 mg of L-dopa (Chiesi Farmaceutici)

  **Posology:** As adjunctive “as needed” therapy, the recommended unit dose is 1 ml of solution (251.2 mg/day of L-dopa); more than two administrations/day are not recommended.
Side effects of levodopa

Treatment:
atypical antipsychotics (clozapine, quetiapine)
Pharmacological interactions
Prarmacological interaction with *levodopa*

**Negative interactions**

- **Typical antipsychotics:** haloperidol
- **Non-selective MAO inhibitors:** phenelzine and tranylcypromine or selective for MAO-A: moclobemide (foods containing tyramine)
- **Tricyclics:** potentiate the effects of anticholinergics
Complications associated with L-DOPA therapy

- **Motor fluctuations**
  Wearing-off deterioration of end-of-dose response
  ‘On-off’, ‘on’ response deterioration, no ‘on’ response

- **Involuntary movements**
  peak dose or biphasic dyskinesia
  peak dose dystonia

- **Neuropsychiatric complications**
  psychosis, hallucinations, confusion, depression

- **Non-motor complications**
  autonomic dysfunctions
Dyskinesia induced by L-DOPA

UNTREATED

STABLE

WEARING-OFF

ON-OFF

Percent Responding

Percent Responding

0 0.4 0.8 1.2 1.6

0 0.4 0.8 1.2 1.6

mg/Kg

mg/Kg
- **Progression of dopamine neuron degeneration**

- **Pulsatile stimulation of dopaminergic receptors**
1. Neurotrasmettitore che si lega a un recettore

2. Proteina G che attiva l'adenilato ciclasi e produce AMPc

3. AMPc che attiva la PKA, la quale fosforila la proteina CREB

4. La proteina CREB modula la trascrizione dei geni

5. I geni codificano proteine che influenzano la trasmissione dei segnali
Terapy of dyskinesia

- Adjustment of L-DOPA dose
- Amantadine
- Clozapine
- DBS (deep brain stimulation)
Duodopa

Avoid pulsatile stimulation of dopaminergic receptors

Duodenal infusion of levodopa / carbidopa (Duodopa®)
Gel for continuous intestinal administration based on levodopa and carbidopa (4: 1 ratio)

*In patients with advanced PD (stage 4-5), who are not effectively controlled with standard oral therapy*