Parkinson Disease
AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS,

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1817.
Tremore
Postura Inclinata
Mimica facciale a "maschera"
Rigidità
Tremori
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
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

Alfa synuclein ad Lewy bodies
Involved Neurotransmitters a part from dopamine

- **Serotonin**: 5-HT_{1A}R agonists ↓ glutamatergic release
- **Glutamate**: mGlu5 NAMs ↓ NMDAR activity
- **Histamine**: H_{2}R antagonists ↑ ACh release
- **Acetylcholine**: Nicotinic receptor agonists ↑ dopamine release
- **Noradrenaline**: α_{2A} adrenergic receptor antagonists ↓ striatal output
- **Noradrenaline**: LC degenerates in PD; NA reuptake inhibitors ↑ NA levels
- **Adenosine**: A_{2A}R antagonists ↑ D_{2}R activity
- **GABA**: GAD ↑ GABA levels in STN
- **Acetylcholine**: NBM and PPN degenerate in PD; AChase inhibitors ↑ ACh levels
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.
Mechanisms
Environmental Factors
- Rotenone
- Paraquat
- MPTP

Mitochondrial dysfunction
mtDNA mutations
Misfolded proteins

Oxidative stress
ROS production
excitotoxicity

Death of DA Neurons in SNpc

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

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. Interaction with potential neurotoxic proteins
2. Dopamine neuron cell death
3. Motor impairment

Non-toxic α-synuclein conformations

Lewy bodies

Chaperone depletion
Oxidative stress
Oxidative Stress

ROS

\[ \cdot \text{O}_2^- \quad \cdot \text{OH} \quad \text{H}_2\text{O}_2 \]

ATTACCANO GRUPPI SH (PROTEICI)
IMPEDISCONO GENERAZIONE ATP DA MITOCONDRI
GENERANO AGENTI OSSIDANTI H$_2$O$_2$
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>ANTIOSSIDANTI (neutralizzano o comunque limitano l’attività dei radicali liberi)</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**
  \[ 2\text{GSH} + \text{H}_2\text{O}_2 \rightarrow \text{GS-SG} + 2\text{H}_2\text{O} \]
  \[ \text{ROOH} + 2\text{GSH} \rightarrow \text{ROH} + \text{GS-SG} + \text{H}_2\text{O} \]
Environmental Factors:
- Rotenone
- Paraquat
- MPTP

Oxidative stress
ROS production
Excitotoxicity

Mitochondrial dysfunction
mtDNA mutations
Misfolded proteins

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PD
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 $\text{Ca}^{2+}$ concentration ($\text{Ca}^{2+}$ 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 $\text{Ca}^{2+}$ 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 $\text{Ca}^{2+}$ 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
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.
(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.