Etiology & Pathogenesis of Parkinson Disease

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Conflict of Interest Statement

No drug company pays me any money
Outline of Etiology & Pathogenesis of Parkinson Disease

- History
- Definition
- Pathology
- Epidemiology
- Pathogenesis & Etiology
- Why do we care?
Why Study Etiology & Pathophysiology?
Parkinson Disease Does Not Spare Anyone
History of Parkinson Disease (PD)

- 1817: James Parkinson describes “Shaking Palsy”
- 1904 & 1905: Importance of the diagnosis of paralysis of vertical movements of the eyes (Posey & Spiller)
- 1912: German pathologist Frederick Lewy describes neuronal cytoplasmic inclusions = Lewy bodies
- 1951: Apomorphine injection improved symptoms in a PD patient (Schwab)
- 1952: Intra-operative DBS for surgical destruction of GPi and thalamus (Spiegel)
- 1960: Parkinson disease is a state of dopamine deficiency (Ehringer & Hornykiewicz)
- 1961: First trial of IV levodopa in a PD patient (Birkmayer)
- 1964: Progressive supranuclear palsy: clinical and pathologic description (Steele, Richardson, Olszewski)
- 1968: Corticodentatonigral degeneration with neuronal achromasia (Rubeiz, Kolodny, Richardson)
- 1991: DBS of ventral intermediate thalamic (Vim) nucleus (Benabid)
- 1995: DBS for subthalamic nucleus (STN) in PD (Limousin)
**Idiopathic Parkinson Disease (PD)**

- **Definition of PD:**
  - Parkinsonism
  - Degeneration of dopaminergic neurons in the substantia nigra pars compacta
  - Lewy bodies in degenerating neurons

- **Parkinsonism: 2/3 Cardinal Symptoms**
  - Tremor at rest
  - Bradykinesia
  - Rigidity

- **Rule out Parkinson Plus Syndromes (atypical parkinsonism):**
  - 10% of parkinsonian patients
  - Rapidly disabling
  - Poorly treatable
Differential Diagnosis of Parkinsonism

**IPD vs Parkinson Plus Syndromes**

- **Synucleinopathy**
  - Multiple system atrophy: (oligodendroglial intracytoplasmic inclusions)
    - Shy-Drager Sd (P + autonomic Sx)
    - Olivo-ponto-cerebellar atrophy-OPCA (P + cerebellar Sx)
    - Striatonigral degeneration (P + poor response to levodopa)

- **Progressive supranuclear palsy**
  - (P + early imbalance + eyes movement abnormalities)

- **Corticobasal ganglionic degeneration-CBGD**
  - (P + unilateral dystonia + cortical sensation loss)

- **Parkinsonism + early dementia:**
  - Alzheimer disease + Parkinsonism
  - Diffuse Lewy body disease
  - Vascular dementia + Parkinsonism (white matter disease?)

- **Lower body Parkinsonism:**
  - Vascular Parkinsonism (white matter disease?)
  - Normal pressure hydrocephalus
Gross Pathology in Parkinson Disease

SNc

Normal midbrain  Parkinson disease

Extent of injury needed to cause parkinsonian signs?
**PD Score vs % Residual Cell Count**

Threshold of nigral cell loss

~14 to 23%

$r = -0.87$

$p < 0.0001$

$n = 14$

Threshold of striatal dopamine loss ~14 to 37%

$\text{PD Score vs } \% \text{ Residual Striatal Dopamine}$

$r = -0.77$

$p = 0.016$

$n = 9$

Low nigrostriatal reserve for motor parkinsonism in nonhuman primates

Samer D. Tabbal a, LinLin Tian a, Morvarid Karimi a, Christopher A. Brown a, Susan K. Loftin a, Joel S. Perlmutter a,b,c,d,e,*

Results

The percent of residual cell counts in lesioned nigra correlated linearly with the parkinsonism score at 2 months ($r = -0.87$, $p < 0.0001$). The parkinsonism score at 2 months correlated linearly with the percent residual striatal dopamine ($r = -0.77$, $p = 0.016$) followed by a flooring effect once nigral cell loss exceeded 50%. A reduction of about 14 to 23% of nigral neuron counts or 14% to 37% of striatal dopamine was sufficient to induce mild parkinsonism.
Alpha-Synuclein

- Normal α-synuclein:
  - Location: presynaptic membranes and vesicular structures
  - Function: synaptic vesicle recycling?

- Aggregated α-synuclein:
  - Major component of Lewy bodies (with ubiquitin) & Lewy neurites
  - α-synuclein oligomer can transf ect neurons, mediating toxicity

Adapted from Lansbury & Brice 2002
Lewy Bodies, Neurites & Plaques

Lewy Bodies’ main components are ubiquitin & α-synuclein.

α-synuclein aggregates can be:
- Cytoplasmic (soma): Lewy Bodies
- Axonal: Lewy neurites (d, e, f)
- Extracellular: Lewy plaques (g)
  - Aβ core surrounded by α-synuclein dystrophic neurites

**Braak Staging of PD: Spread of Lewy Body**

1) Anterior olfactory n.
   Dorsal motor nuclei:
   - glossopharyngeal n.
   - vagal n.
2) Ascends in the brain stem:
   - caudal raphe nuclei
   - gigantocellular reticular nucleus
   - coeruleus–subcoeruleus complex
3) Substantia nigra pc
4) Anteromedial temporal mesocortex
5) Neocortex high order sensory association & prefrontal areas
6) First order sensory association/premotor areas & primary sensory/motor fields
(Braak H, *Neurobiology of Aging* 2003)
Behavior of Lewy Bodies

Lewy bodies contain > 70 molecules, including:
- calbindin, complement proteins, microfilament subunits, tubulin, microtubule associated protein 1 and 2, and Pael-R (a parkin substrate protein)

Lewy bodies formation can spread from neuron to neuron in animal models and humans (Luk KC, Science 2012)
- Fetal tissue dopaminergic neurons transplanted in the striatum of humans develop Lewy bodies (Kordower, Nat Med 2008)

Lewy bodies may protect neurons from degeneration (Wakabayashi K et al, Neuropathology 2007; Bodner RA et al, Proc Natl Acad Sci 2006)

Braak Staging:
- Reflects extent of spread, may not reflect sequence of spread
- No correlation between Braak stage and clinical severity of PD (Burke RE, Ann Neurol 2008)

No Lewy bodies in Parkinson syndrome associated with Park 2 gene or LRRK2 gene mutations
Sites of Neurodegeneration in Parkinson Disease:

- Substantia nigra pars compacta
- Substantia innominata
- Amygdala
- Ventral tegmental area
- Locus ceruleus
- Raphe nuclei
- Dorsal motor nucleus of vagus nerve
- Intermediolateral column/Sympathetic ganglia

## Prevalence of PD in the World

Table 7: Prevalence (millions) of selected conditions by WHO region, 2004

<table>
<thead>
<tr>
<th>Condition</th>
<th>World</th>
<th>Africa</th>
<th>The Americas</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
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</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>13.9</td>
<td>3.0</td>
<td>0.5</td>
<td>1.1</td>
<td>0.6</td>
<td>5.0</td>
<td>3.8</td>
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<td>HIV infection</td>
<td>31.4</td>
<td>21.7</td>
<td>2.8</td>
<td>0.5</td>
<td>2.0</td>
<td>3.3</td>
<td>1.0</td>
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<tr>
<td>Intestinal nematodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>– high intensity infection</td>
<td>150.9</td>
<td>57.6</td>
<td>5.8</td>
<td>8.5</td>
<td>0.0</td>
<td>37.7</td>
<td>41.1</td>
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<tr>
<td>Protein-energy malnutrition:</td>
<td></td>
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<td></td>
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<tr>
<td>– wasting (ages 0-4)</td>
<td>56.2</td>
<td>13.7</td>
<td>1.4</td>
<td>6.5</td>
<td>0.9</td>
<td>27.0</td>
<td>6.7</td>
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<tr>
<td>– stunting (ages 0-4)</td>
<td>182.7</td>
<td>51.9</td>
<td>9.5</td>
<td>18.6</td>
<td>4.0</td>
<td>76.5</td>
<td>22.0</td>
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<td>Iron-deficiency anaemia</td>
<td>1159.3</td>
<td>193.8</td>
<td>66.4</td>
<td>88.5</td>
<td>77.7</td>
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<td>Diabetes mellitus</td>
<td>220.5</td>
<td>9.7</td>
<td>46.4</td>
<td>17.9</td>
<td>45.4</td>
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<td>Unipolar depressive disorders</td>
<td>151.2</td>
<td>13.4</td>
<td>22.7</td>
<td>12.4</td>
<td>22.2</td>
<td>40.9</td>
<td>39.3</td>
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<td>Bipolar affective disorder</td>
<td>29.5</td>
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<td>4.1</td>
<td>2.1</td>
<td>4.4</td>
<td>7.2</td>
<td>8.9</td>
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<td>Schizophrenia</td>
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<td>2.1</td>
<td>3.9</td>
<td>1.9</td>
<td>4.4</td>
<td>6.2</td>
<td>7.9</td>
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<td>Epilepsy</td>
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<td>7.7</td>
<td>8.6</td>
<td>2.8</td>
<td>4.1</td>
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<td>Alcohol use disorders</td>
<td>125.0</td>
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<td>24.2</td>
<td>1.1</td>
<td>26.9</td>
<td>21.5</td>
<td>47.3</td>
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<tr>
<td>Alzheimer and other dementias</td>
<td>24.2</td>
<td>0.6</td>
<td>5.0</td>
<td>0.6</td>
<td>7.6</td>
<td>2.8</td>
<td>7.4</td>
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<td>Parkinson disease</td>
<td>5.2</td>
<td>0.2</td>
<td>1.2</td>
<td>0.2</td>
<td>2.0</td>
<td>0.7</td>
<td>1.0</td>
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<tr>
<td>Migrainea</td>
<td>324.1</td>
<td>12.6</td>
<td>59.7</td>
<td>16.2</td>
<td>77.3</td>
<td>70.3</td>
<td>87.5</td>
</tr>
</tbody>
</table>
Epidemiology of Parkinson Disease

- Estimated 1 million PD patients in the USA (~1/300)
- Prevalence on the rise with aging baby boomers (expected to triple by 2050)

Etiology: Genetic vs Environmental?

- Man/Woman ratio ~ 2:1
- Age: 10/100,000 by age 50, 200/100,000 by age 80
- Race: Whites ~ Hispanics > Blacks/Asians (Willis 2010)
- Urban > Rural (Willis 2010)
- Chemicals: pesticides, hydrocarbons, manganese, MPTP (1983)
- Hx of concussion
- Low vitamin D
- Occupation: agriculture, carpenters, cleaners, teachers, health care workers, exposure to metals, welders…
- Genes: PARK 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, … 20 and counting!
  - Only 10% of Parkinson disease is familial

Neuro-protective factors:

- Caloric restriction, antioxidants (?), smoking (???), caffeine (?), alcohol (?), …
County level age- and race-standardized incidence (per 100,000) of Parkinson Disease Medicare Data 2003

“Parkinson disease belt”

Wright-Willis A et al, Neuroepidemiology 2010; vol 34:143–151
### Table 1. PARK-designated PD-related loci

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene locus</th>
<th>Disorder</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Status and remarks</th>
<th>Mode of identification</th>
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<tbody>
<tr>
<td>PARK1</td>
<td>4q21-22</td>
<td>EOPD</td>
<td>AD</td>
<td>SNCA</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK2</td>
<td>6q25.2-q27</td>
<td>EOPD</td>
<td>AR</td>
<td>Parkin</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<tr>
<td>PARK3</td>
<td>2p13</td>
<td>Classical PD</td>
<td>AD</td>
<td>Unknown</td>
<td>Unconfirmed; may represent a risk factor; gene not found since first described in 1998</td>
<td>Linkage analysis</td>
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<td>PARK4</td>
<td>4q21-q23</td>
<td>EOPD</td>
<td>AD</td>
<td>SNCA</td>
<td>Erroneous locus (identical to PARK1)</td>
<td>Linkage analysis</td>
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<td>PARK5</td>
<td>4p13</td>
<td>Classical PD</td>
<td>AD</td>
<td>UCHL1</td>
<td>Unconfirmed (not replicated since described in 1998)</td>
<td>Functional candidate gene approach</td>
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<tr>
<td>PARK6</td>
<td>1p35-p36</td>
<td>EOPD</td>
<td>AR</td>
<td>PINK1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK7</td>
<td>1p36</td>
<td>EOPD</td>
<td>AR</td>
<td>DJ-1</td>
<td>Confirmed</td>
<td>Linkage analysis</td>
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<tr>
<td>PARK8</td>
<td>12q12</td>
<td>Classical PD</td>
<td>AR</td>
<td>LRRK2</td>
<td>Confirmed; variations in LRRK2 gene include risk-conferring variants and disease-causing mutations</td>
<td>Linkage analysis</td>
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<tr>
<td>PARK9</td>
<td>1p36</td>
<td>Kufor-Rakeb syndrome; atypical PD with dementia, spasticity, and supranuclear gaze palsy</td>
<td>AR</td>
<td>ATP13A2</td>
<td>Confirmed; but complex phenotype that would not be mistaken for early-onset or classical parkinsonism</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK10</td>
<td>1p32</td>
<td>Classical PD</td>
<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus; gene unknown since first described in 2002</td>
<td>Linkage analysis</td>
</tr>
<tr>
<td>PARK11</td>
<td>2q36-27</td>
<td>Late-onset PD</td>
<td>AD</td>
<td>Unconfirmed; not GIGYF2</td>
<td>Not independently confirmed; possibly represents a risk factor; gene not found since first described in 2002</td>
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<td>PARK12</td>
<td>Xq21-q25</td>
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<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus; possibly represents a risk factor; gene not found since first described in 2003</td>
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<td>PARK13</td>
<td>2p12</td>
<td>Classical PD</td>
<td>AD or risk factor</td>
<td>HTRA2</td>
<td>Unconfirmed</td>
<td>Candidate gene approach</td>
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<td>PARK14</td>
<td>22q13.1</td>
<td>Early-onset dystonia-parkinsonism</td>
<td>AR</td>
<td>PLA2G6</td>
<td>Confirmed</td>
<td>Linkage analysis (homozygosity mapping)</td>
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<tr>
<td>PARK15</td>
<td>22q12-q13</td>
<td>Early-onset parkinsonian-pyramidal syndrome</td>
<td>AR</td>
<td>FBX07</td>
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<td>Linkage analysis</td>
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<tr>
<td>PARK16</td>
<td>1q32</td>
<td>Classical PD</td>
<td>Risk factor</td>
<td>Unknown</td>
<td>Confirmed susceptibility locus</td>
<td>Genome-wide association studies</td>
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<td>PARK17</td>
<td>16q11.2</td>
<td>Classical PD</td>
<td>AD</td>
<td>VPS35</td>
<td>Confirmed</td>
<td>Exome sequencing</td>
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<td>PARK18</td>
<td>3q27.1</td>
<td>Classical PD</td>
<td>AD</td>
<td>EIF4G1</td>
<td>Unconfirmed; recently published (Chartier-Harlin et al. 2011)</td>
<td>Linkage analysis</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive.
## Genes & Loci Associated with Familial PD

<table>
<thead>
<tr>
<th>Approved Symbol</th>
<th>Approved Name</th>
<th>Previous Symbols</th>
<th>Synonyms</th>
<th>Chromosome</th>
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<tr>
<td>SNCA</td>
<td>synuclein, alpha (non A4 component of amyloid precursor)</td>
<td>PARK1, PARK4</td>
<td>NACP, PD1, alpha-synuclein</td>
<td>4q21.3-q22</td>
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<tr>
<td>PARK2</td>
<td>parkin RBR E3 ubiquitin protein ligase</td>
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<td>PDJ, AR-1P, parkin</td>
<td>6q25.2-q27</td>
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<td>PARK3</td>
<td>Parkinson disease 3 (autosomal dominant, Lewy body)</td>
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<td></td>
<td>2p13</td>
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<tr>
<td>UCHL1</td>
<td>ubiquitin carboxyl-terminal esterase L1 (ubiquitin thiolesterase)</td>
<td>PARK5</td>
<td>PGP9.5, Uch-L1</td>
<td>4p13</td>
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<td>PINK1</td>
<td>PTEN induced putative kinase 1</td>
<td>PARK6</td>
<td></td>
<td>1p36.12</td>
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<tr>
<td>PARK7</td>
<td>parkinson protein 7</td>
<td>DJ-1, DJ1</td>
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<td>LRRK2</td>
<td>leucine-rich repeat kinase 2</td>
<td>PARK8</td>
<td>ROCO2, DKFZp434H2111, FLJ45829, RIPK7</td>
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<td>ATP13A2</td>
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<td>PARK10</td>
<td>Parkinson disease 10 (susceptibility)</td>
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<td>AAOPD</td>
<td>1p32</td>
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<td>PARK11</td>
<td>Parkinson disease 11 (autosomal recessive, early onset)</td>
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<td>2q36-q37</td>
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<td>PARK12</td>
<td>Parkinson disease 12 (susceptibility)</td>
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<td>Xq21-q25</td>
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<td>HTRA2</td>
<td>HtrA serine peptidase 2</td>
<td>PRSS25</td>
<td>OMI, PARK13</td>
<td>2p13.1</td>
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<td>PLA2G6</td>
<td>phospholipase A2, group VI (cytosolic, calcium-independent)</td>
<td>iPLA2, PNPLA9, PARK14, iPLA2beta, NBIA2</td>
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<td>FBXO7</td>
<td>F-box protein 7</td>
<td>FBX7, Fbx, PARK15</td>
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<td>PARK16</td>
<td>Parkinson disease 16 (susceptibility)</td>
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<td>VPS35</td>
<td>vacuolar protein sorting 35 homolog (S. cerevisiae)</td>
<td>FLJ10752, MEM3, PARK17</td>
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<td>EIF4G1</td>
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<td>EIF4G, EIF4F</td>
<td>p220, PARK18</td>
<td>3q27.1</td>
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</tbody>
</table>
Pathogenesis of Parkinson Disease

- Protein handling: ubiquitin & α-synuclein
- Mitochondrial dysfunction
- Oxidative stress: free radicals & iron
- Nitrosative stress: Nitric oxide, peroxynitrite & protein nitration
- Inflammation
- Excito-toxicity: glutamate & calcium
- Deficiency of trophic factors
- Apoptosis (?)
**Ubiquitin-Proteasome System (UPS)**

(activating)

E1

Ub

+ ATP

E1-Ub

E2

Ub

E2-Ub

DUB

UCH-L1

26S proteasome

Poly-ubiquitination

Mono-ubiquitination

Abnormal protein

Mutant/damaged/misfolded

Normal protein

Short-lived

K29 or K48 poly-Ub

K63 poly-Ub

Non-proteasomal functions

Abnormal

Normal

UCH-L1=Ubiquitin carboxyl-terminal hydrolase/esterase L1

Adapted from Glickman & Ciechanover 2002
Effects of Genes on the UPS & Protein Degradation

- PARK 1 (& PARK 4) code for α-synuclein: mutations cause natively unfolded α-synuclein protein to alter its secondary structure and self-aggregate
- The proteins Parkin (from PARK 2), Pink1 (from PARK 6) and DJ-1 (from PARK 7) bind to each other to form a complex that promotes degradation of unfolded or misfolded proteins via the UPS
- PARK 9 mutations: ATP13a2 deficiency can cause lysosomal dysfunction

- Potential drug that may reduce α-synuclein in Phase I study
  - Nilotinib: tyrosine kinase inhibitor that interacts with α-synuclein
  - PRX002 vaccine: anti-α-synuclein antibodies
  - PD01A vaccine: induces anti-α-synuclein antibodies production
Mitochondrial Dysfunction in PD

- Complex I activity is decreased by 32 to 38% in substantia nigra
- Complex I inhibition induces Lewy body-like inclusions in vivo
- MPTP and rotenone inhibit complex I
  - Rotenone mice model: develop pathologically with fibrillary cytoplasmic inclusions staining for ubiquitin and α-synuclein
- Mitochondrial dysfunction increases oxidative and nitrosative stress
- Parkin, PINK1 and DJ-1 contribute to normal mitochondrial function
- Mitochondrial membrane potential and intracellular ATP levels are significantly decreased in skin fibroblasts of patients with LRRK2 G2019S mutation
- Mitochondrial dysfunction promotes α-synuclein aggregation
**Oxidative Stress**

- Hypothesis: inappropriate production of reactive oxygen species (free radicals) leads to neurodegeneration

- Dopamine metabolic pathways $\rightarrow$ hydrogen peroxide, superoxide anions and hydroxyl radicals $\rightarrow$ toxic lipid peroxidation injuring cell membranes $\rightarrow$ neuronal degeneration

- Neuromelanin:
  - made of 5,6-dihydroxyindole monomers
  - Protects neurons: Excess dopamine and DOPA molecules are oxidized by iron catalysis $\rightarrow$ quinones and semiquinones $\rightarrow$ phagocytosed and stored as neuromelanin
  - Injures neurons: dying neurons may release neuromelanin, leading to chronic inflammation

- Iron plays a critical role in oxidative metabolism
  - is increased by about 50% in substantia nigra of PD brains relative to controls
  - is a cofactor in the synthesis of neurotransmitters
Nitrosative stress

- Nitric oxide, peroxynitrite → protein nitration
- Nitric oxide:
  - is a free radical
  - is increased in the brains of patients with PD
  - attacks disulfide isomerase, an aggregation-preventing chaperone protein that is normally responsible for unfolding and transport of proteins → misfolding of proteins
Pathophysiology of PD: Synucleinopathy

- Complex-I inhibition (toxins)
- mtDNA alterations
- PINK1
- Oxidative stress
- α-synuclein aggregation
- DJ-1
- Oxidative stress
- Parkin
- UCH-L1
- Dopamine oxidation
- Dopamine
- UPS
The Role of Inflammation in PD

- Inflammation unlikely the etiology of PD but it may contribute to neuronal injury

- Cyclooxygenase-2:
  - the rate-limiting enzyme in prostaglandin E2 synthesis
  - is upregulated in patients with PD and in the MPTP mouse model of PD. Cyclooxygenase-2 inhibition prevents the formation of potentially toxic dopamine-quinones in MPTP mice and possibly in patients with PD.

- In a PET study, microglial activity in patients with PD correlated with decreased density of dopamine transporter.

- Infiltration of CD4+ T-lymphocytes contributed to neuronal cell death in a mouse model of PD.
Deficiency of Trophic Factors

- GDNF & BDNF levels are decreased in PD patients
  - Is this a cause or result of neuronal degeneration?
- Intraventricular GDNF: did not reach target neurons
- Palirodene: failed
- Exercise is very likely neuroprotective
  - in part through increasing neurotrophic factors?
- Fasting increases neurotrophic factors in animals
- Potential neuroprotective factors in on-going studies:
  - Neurturin (CERE-120)
    - Putaminal and/or nigral AAV-2 vector encoding for a neurotrophic factor
  - Cogane (PYM50028)
    - Neurotrophic factor modulator, oral
  - Davunetide
    - Neurotrophic protein, nasal
  - GM1 ganglioside
    - Potentiates BDNF and NGF
Which Pathophysiology is the Most Significant One in PD

- Mitochondrial dysfunction and Oxidative stress:
  - Antioxidants have failed so far, including: MAO inhibitors (selegiline, rasagiline), vitamin E (up to 2,000 IU/day), Co-enzyme Q10 (up to 2400 mg/day), mitoquinone ...
  - Uric acid (studies ongoing; risk of gout?)

- Inflammation:
  - Pioglitazone (microglia inhibitor) and minocycline (anti-inflammatory drug)

- Excito-toxicity (glutamate/calcium):
  - Riluzole failed
  - Anti-glutamate drugs often cause hallucinations

- Apoptosis: CEP-1347 and immunophilin failed
**Which Pathophysiology is the Most Significant One in PD**

- Do we need a more powerful drugs for neuroprotection in PD?
  - More powerful antioxidants, anti-inflammatory drugs, trophic factors, anti-apoptotic drugs …

- Are we climbing the wrong tree/hypothesis?
  - Dopaminergic cell transplantation was a wrong tree to climb
  - Do we need an “anti-α-synuclein approach”?
    - Nilotinib? Phenylbutyrate? Blockers of α-synuclein spread?

- Are we intervening too late? YES, YES and YES!

- Parkinson disease is not ONE disease
  - Need for identifying “types of Parkinson disease” by pathophysiology
  - Do we need to use a combination of potential neuroprotective drugs?
  - Should we quit using hydrocarbons?
Carboxyfullerene (C3): “The Radical Sponge”

- C3:
  - has tremendous anti-oxidant and some anti-inflammatory effects
  - can be given orally

Carboxyfullerene Neuroprotection Postinjury in Parkinsonian Nonhuman Primates

Laura L. Dugan, MD,1,2,3 LinLin Tian, PhD,3 Kevin L. Quick, PhD,3 Josh I. Hardt, PhD,3 Morvarid Karimi, PhD,3 Chris Brown,3 Susan Loftin,3 Hugh Flores,3 Stephen M. Moerlein, MD,4,5 John Polich, PhD,6 Samer D. Tabbal, MD,3 Jonathan W. Mink, MD, PhD,7 and Joel S. Perlmutter, MD3,4,8,9

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Carboxyfullerene
Parkinsonism Score & Kinematics
Carbofullerene

A

FDOPA $K_{occ}$ Ratio (lesioned/unlesioned)

- Pre-MPTP
- After 2 months of treatment

B

DTBZ BP Ratio (lesioned/unlesioned)

- Pre-MPTP
- After 2 months of treatment

**Placebo**

- Dopamine (ng/g brain)

- Th positive cell counts - Lesioned side / Unlesioned side (%)

**C3**
...And Above All...

Don't EVER give up!