Recent Advances in the cause and treatment of Parkinson disease

Anthony Schapira
Head of Dept. Clinical Neurosciences
UCL Institute of Neurology
UCL
SOME BACKGROUND…
The graph shows the incidence rate of a particular condition over age, with data from various regions:

- Hawaii (ref. 15)*
- Italy (ref. 24)
- Rochester (ref. 23)
- Rotterdam (ref. 12)
- Manhattan (ref. 16)
- London (ref. 22)
- Spain (ref. 11)
- Taiwan (ref. 26)
- China (ref. 25)

The incidence rate is expressed per 100,000 person years.
Pathological changes in PD

A. Normal
B. Parkinson’s Disease

C.

- Lewy Body
- Synuclein
- Ubiquitin
Disease Progression
Evolution of Lewy Body Pathology in PD
Aetiology
CAUSE - ENVIRONMENT
Environmental causes of PD
Modifying factors for PD risk

- Pesticides, herbicides, farming, rural living
- Solvent exposure
- Doctors, teachers
- Red hair
- Low vitamin D
- Smoking
- Coffee
- NSAIDS
- Isradipine
- Black hair
- High urate
Environment & Genetics in disease

ENVIRONMENT

GENETICS

DISEASE
Environment & Genetics in disease

ENVIRONMENT  GENETICS  DISEASE
CAUSE - GENETICS
Genetic causes of PD

- GWAS – SNCA, tau, HLA-DR2, LRRK2
- Alpha-synuclein mutations – point, multiplications
- Parkin mutations
- DJ1 mutations
- PINK1 mutations
- LRRK2 mutations
- Others: HtrA2, UCHL1, ATP13A2, PLA2G6, GIGYF2
- Glucocerebrosidase: 7-20 fold increased risk
PD PATHOGENESIS

- Mitochondria
- Protein folding, aggregation, propagation
- Lysosomes
Braak hypothesis for spread of Lewy bodies

Braak et al., 2003
Fetal graft cells develop PD pathology

Kordower et al Nat Med 2008
Fetal graft cells develop PD pathology

Kordower et al Nat Med 2008
PD PATHOGENESIS

- Mitochondria
- Protein folding, aggregation, propagation
- Lysosomes
Glucocerebrosidase

- AuR, >300 mutations, ↓GBA activity
- Gaucher disease, lysosomal enzyme
- Commonest in Ashkenazi Jews
- Typical PD, mean age onset 55y, FH in 24%*
- Lewy body positive: 4.5 fold increase in GBA mutations in LB-PD in QS PDBB (Neumann Brain 2009)
- Lifetime risk for PD in GD patients ~20x (Bultron J Inh Met Dis 2010)
GCase in PD Brain

- 58%* ↓ GCase in GBA mutation positive SNc
- 48%* ↓ GCase in GBA mutation positive striatum

*p<0.01
GCase in PD Brain

- 58%* ↓ GCase in GBA mutation positive SNc
- 48%* ↓ GCase in GBA mutation positive striatum
- 33%* ↓ GCase in GBA mutation negative sporadic PD SNc

*p<0.01
The GCase - alpha-synuclein connection

Schapira Lancet 2014
Symptomatic treatments for Parkinson disease
Drug treatment of Parkinson’s disease

- L-dopa
- Decarboxylase inhibitors – carbidopa, benserazide
- MAO-B inhibitors – selegiline, rasagiline
- COMT inhibitors – entacapone, tolcapone
- Combination forms – Stalevo
- Controlled release – Sinemet CR
- Dispersible – Madopar dispersible
- Liquid formulations – L-dopa methyl ester
- Intraduodenal administration - DuoDopa
- Ropinirole
- Pramipexole
- Pergolide
- Bromocriptine
- Cabergoline
- Extended release – Requip XL
- Transdermal administration – NeuPro
- Subcutaneous infusion - apomorphine
Safinamide

- Reversible MAOB inhibitor
- May have Na-channel, anti-glutamatergic activity
- Once daily 50-100mg
- Adjunct to levodopa (+) or dopamine agonist
- Reduces OFF-time, improves ON-time without increasing troublesome dyskinesia.
Non-dopaminergic approaches to the treatment of Parkinson’s disease

- Motor symptoms – amantadine, anticholinergics
- Dementia – cholinesterase inhibitors
- Psychosis – atypical antipsychotics
- Neuropsychiatric – anxiolytics, antidepressants
- Somnolence – modafinil
- Autonomic signs – mineralocorticosteroids, oxybutynin
Neuroprotection

Slowing the course of Parkinson disease
Potential therapeutic targets

- Mitochondria: CoQ +/- vit E, creatine, PGC-1α, rasagiline, exenetide
- Anti-oxidants: Fe-chelators, inosine
- LRRK2 kinase inhibitors
- Growth factor stimulants: GDNF, BDNF
- Autophagy/mitophagy stimulants: rapamycin
- Protein disaggregation
- Calcium channel modulators: isradipine
- SNCA modulators
- GBA enhancers – chaperones  

Schapira Lancet 2014
The GCase - alpha-synuclein connection

Schapira Lancet 2014
GCase-alpha-synuclein as a target for PD

Schapira & Gegg PNAS 2013
Hypothesis

• Increasing GCase activity will reduce SNCA levels and slow the progression of PD
• This will be relevant to those with and without PD
Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells

Alisdair McNeill,¹ Joana Magalhaes,¹ Chengguo Shen,² Kai-Yin Chau,¹ Derralyn Hughes,³ Atul Mehta,³ Tom Foltynie,⁴ J. Mark Cooper,¹ Andrey Y. Abramov,⁵ Matthew Gegg¹ and Anthony H.V. Schapira¹
Proof of principle

![Bar chart showing GCase activity (nmol/hour/mg) for different conditions: control/PD, control/PD+, GD, GD+, PD-GBA, PD-GBA+.]
Ambroxol reduces alpha-synuclein levels in cells after 5 days
AN

ESSAY

OF THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF PHYSICIANS.

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