Parkinson's disease: causes & cures

European Parliament, 8 November 2018

S&D

EuChemS European Chemical Society

EFMC European Federation for Medicinal Chemistry

Animal models of Parkinson's disease

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Animal models of PD are essential

- to prove causal links between molecular-genetic defects and brain pathologies relevant to PD.
- to associate the pathologies to specific profiles of motor and non-motor deficits
- to dissect non cell-autonomous mechanisms of disease
- to evaluate potential new therapies
  - pharmacokinetics-pharmacodynamics
  - behavioural & histopathological endpoints
  - translational biomarkers of treatment efficacy

PD models can be produced in many species

Caenorhabditis elegans

Drosophila melanogaster

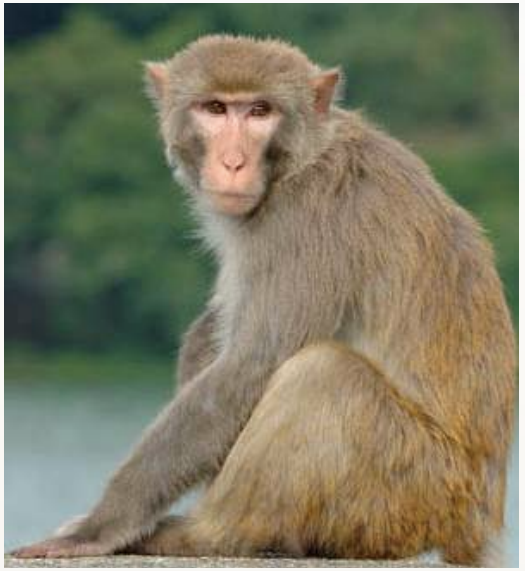
Zebra fish

Mouse

Rat

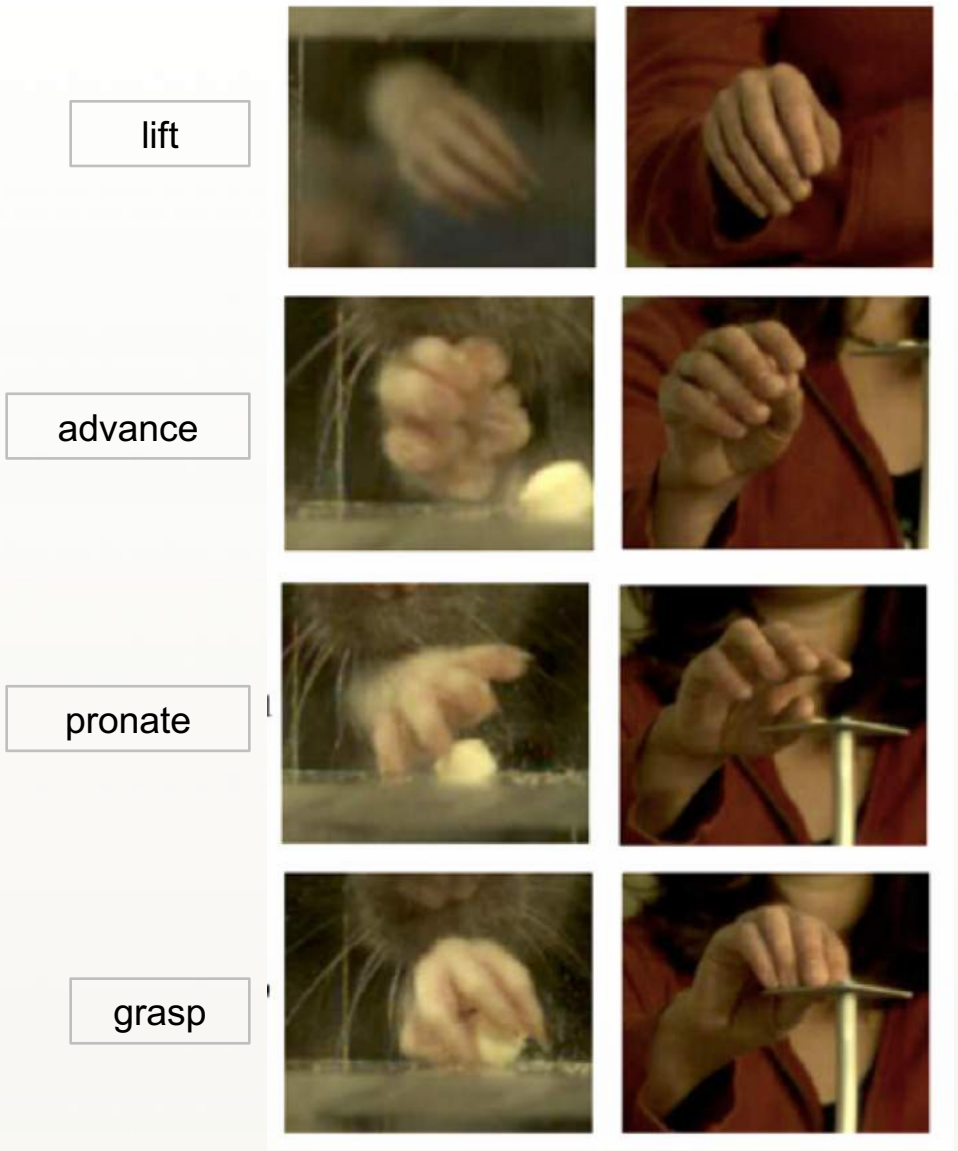
Göttingen minipig

Marmoset



Macaque Rhesus

Rodents show complex movements homologous to those in humans

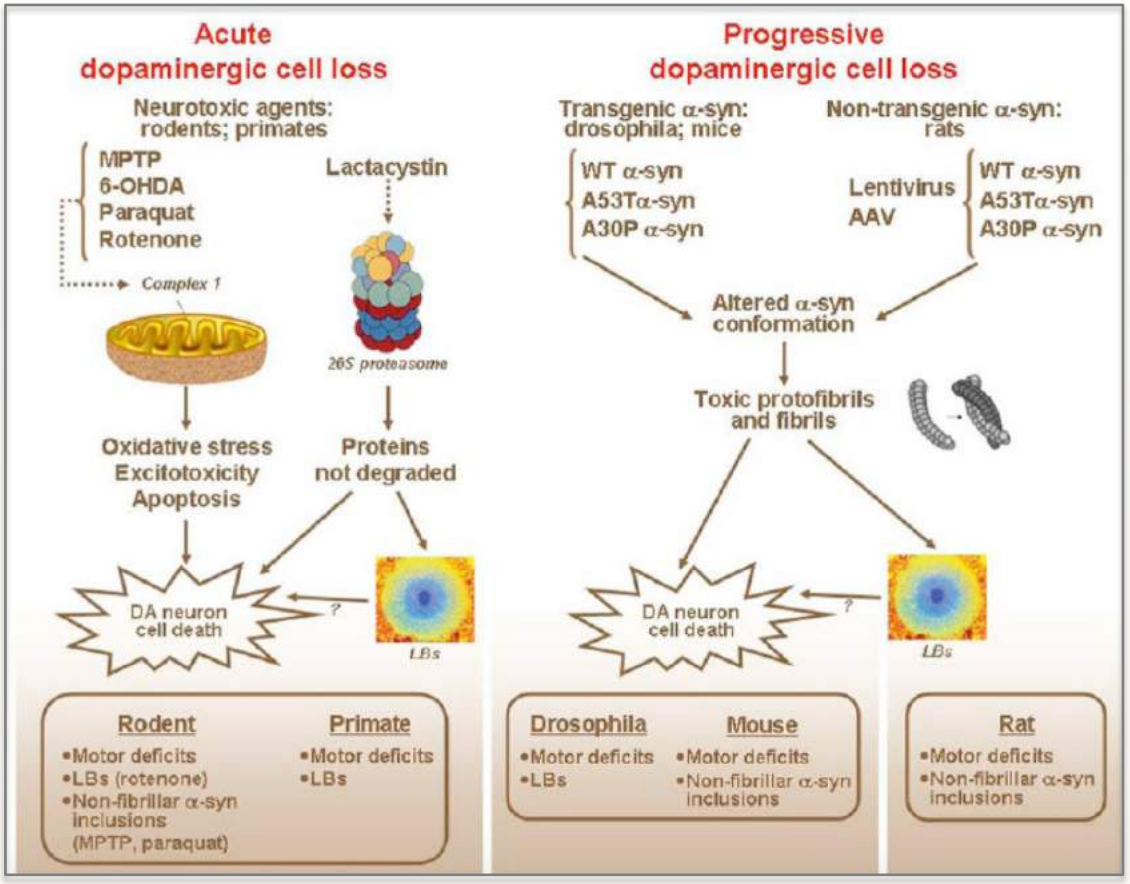


Similar components of skilled reaching in rats and humans indicate homology in release, collection, and manipulation movements.

Sacrey et al. (2009) Behav Brain Res 204:153-161

How can we mimic PD in animals?

No animal model reproduces the entire complexity of PD, but many options are available to mimic key aspects of PD.



Bazzu et al (2010) *CNS & Neurological Disorders Drug Targets* 9:482-90

Two main types of PD models in animals

I. Neurotoxic models

Catecholamine-selective neurotoxins:

- 6-hydroxydopamine
- MPTP

Environmental toxicants:

- Paraquat-maneb (herbicide)
- Rotenone (pesticide)

II. Genetic models

Autosomal recessive PD genes:

- *DJ1* (DJ-1)
- *PINK1* (Pink-1)
- *PARK2* (Parkin)

Autosomal dominant PD genes:

- *LRRK2* (leucine rich repeat kinase 2)
- *SNCA* (alpha-synuclein)

Pros and cons of neurotoxin models

Severe nigrostriatal dopaminergic degeneration

Circuit dysfunctions similar to those in PD (biomarker: basal ganglia oscillations).

High face validity regarding PD symptomatology (motor features and some non-motor features).

Models of choice to study both benefits and complications of symptomatic therapies (including L-DOPA-induced dyskinesia).

Nigrostriatal dopaminergic degeneration is non-progressive.

Lack of intracellular protein aggregates reminiscent of Lewy pathology.

Lack of non-dopaminergic degeneration (unless additional insults are applied).

Not sufficiently validated for the assessment of disease-modifying treatments.

Pros and cons of genetic models

Progressive nigrostriatal dopaminergic degeneration in the best genetic models.

Formation of intracellular protein aggregates reminiscent of Lewy pathology (particularly after inoculation of alpha-synuclein fibrils)

Slowly developing and age-dependent behavioural-pathological phenotypes.

Relevant extranigral* pathology in some models (*brain stem nuclei, hippocampus, cortex).

Lack of nigrostriatal dopaminergic degeneration in many genetic models (e.g. *LRRK2* mutants, *DJ1*, *PINK1*, *PARK2* knockout models)

In some *SNCA* tg models, PD-like features take >12 months to develop (high costs)

Some *SNCA* tg models show confounding pathological features (e.g. degeneration of spinal motoneurons)

Not sufficiently validated for the assessment of symptomatic therapies.

Concluding remarks

An increased understanding of pathological, genetic, and environmental factors underlying PD has prompted the vast repertoire of animal models that are available today.

Today we have unprecedented opportunities to recreate virtually all critical aspects of PD in laboratory animals, and investigators are free to use the animal model most suitable to their research question.

This is a very active and continuously developing area of research (also aided by recent genetic and transgenic technologies).

Animal models of PD are essential to bring about scientific progress and novel therapeutics.