# Parkinson's Disease

*Basal ganglia: function and pathology*

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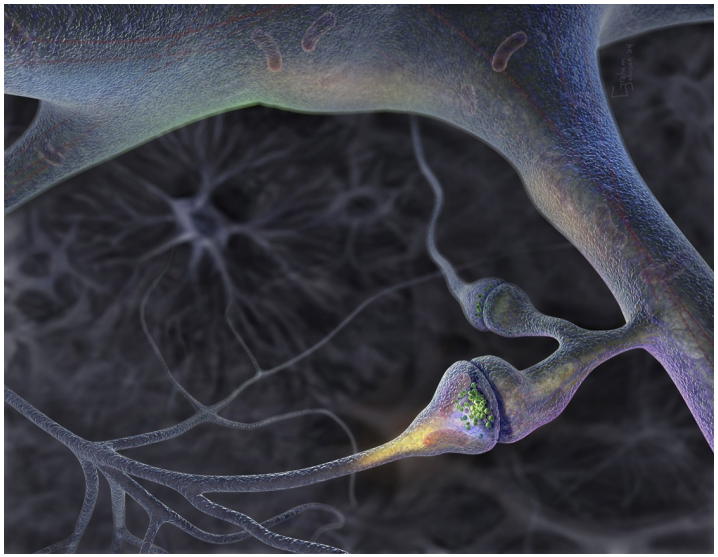
2024



# Parkinson's disease - Question 1

1913: Marcus Guggenheim (Hoffmann-la Roche) isolated the L-DOPA enantiomer from Vicia faba. He ingested the compound and immediately started vomiting as L-DOPA was converted to dopamine, which induces nausea via the medulla oblongata, a CNS region accessible to peripheral dopamine. L-DOPA is now an effective drug for PD, why?

(1 correct answer)

A. L-DOPA is injected in the brain

**B. A compound is co-administered to block L-DOPA to dopamine conversion in the periphery**

C. A modified form of L-DOPA is used that accumulates only in the brain

D. The dose of L-DOPA was adapted to prevent this side effect

# Parkinson's disease - Question 2

L-DOPA treatment is poorly effective in late-stage PD patients because… (indicate all correct answers)

A. L-DOPA does not cross the BBB

B. Dopamine can no more be synthesized from L-DOPA

**C. There is not enough presynaptic vesicles to store dopamine in the striatum**

**D. There is not enough dopamine transporter to recapture dopamine**

E. Striatal neurons have degenerated

**F. Other symptoms appear that do not respond to L-DOPA**

## Parkinson's disease - Question 3

In multiple system atrophy (MSA), there is degeneration of dopaminergic neurons in the substantia nigra which is similar to PD. However, the disease also affects multiple brain regions including medium spiny neurons in the striatum.

MSA patients have Parkinsonian symptoms that respond well to levoDOPA treatment:

A. Vrai
**B. Faux**

## Parkinson's disease: question 4

What is the behavioral effect of **light stimulation** in the striatum of D2R-Cre mice injected with AAV-DIO-ChR2 ?

(1 correct answer)

A. No change in animal motor behavior

B. Constant hyperactivity

C. Transient hyperactivity

**D. Mouse freezing during exposure to light**

## Parkinson's disease: question 5

A toxin is injected in the striatum to induce the selective degeneration of nigrostriatal neurons. The experiment is performed in D1R-Cre mice previously injected with AAV-DIO-ChR2.

**What is the behavioral effect of light stimulation ?**
**(1 correct answer)**

A. Constant hyperactivity

**B. Rescue of parkinsonian bradykinesia observed in these mice**

C. No change in motor activity

D. Development of parkinsonian symptoms

# Parkinson's disease: question 6

Alpha-synuclein pathology propagates across defined pathways in the CNS. What are the implications of this observation ?

Select all the correct statements:

A. **Similar to prion, α-synuclein misfolding is an infectious mechanism**

B. **This shows that the protein may be accessible to therapeutic intervention outside cells**

C. **This mechanism may be either pathological or physiological**

D. This mechanism has no therapeutic implication

# Parkinson's disease: question 7

From the following statements, which one(s) would consider as appropriate conclusions for the article by Luk *et al* ?

A. Injection of α-syn PFF fully replicates PD pathology

B. α-syn aggregates are retrogradely transported in axons

**C. This is the proof that α-syn aggregates can be transported from neuron to neuron in the mouse brain (not completely correct)**

**D. The formation of α-syn fibrils is a critical step in the spreading of the α-syn pathology**

E. α-synuclein is a prion

# Parkinson's disease: question 8

You have discovered that a triplication of a genomic locus containing the α-synuclein gene can lead to autosomal dominant Parkinson's disease (PD), which is characterized by the deposition of Lewy bodies.

Which one(s) of the following statements can you conclude from this finding?

A. **PD can be caused by an overabundance of α-synuclein.**

B. PD is not caused by the loss of the α-synuclein physiological function.

C. **The locus does not contain only the α-synuclein gene. There could be another gene involved in this case.**

D. When overabundant, α-synuclein leads to the formation of Lewy bodies and these aggregates are toxic to the neurons.

# Parkinson's disease: question 9

Why is it important to explore the structure of alpha-synuclein fibrils?
Rank the following statements from "correct" to "possible" to "wrong" ?

1. **It will guide the design of therapeutic antibodies targeting alpha-synuclein pathology.**
2. **Because different types of fibrils may be associated with different diseases (e.g. PD or DLB).**
3. **We could try to identify therapeutic molecules to disassemble these fibrils.**
4. The shape of the fibrils will tell use what is the structure of the α-synuclein protein in normal conditions.

# Parkinson's disease: question 10

The presence of Lewy bodies (LB) is considered as a pathological signature of Parkinson's disease. Rank the following statements from "correct" to "possible" to "wrong" ?

1. **The presence of Lewy bodies is an indicator of α-synuclein misfolding.**
2. **α-Synuclein accumulation in Lewy bodies is a protective mechanism in neurons.**
3. Neurons containing Lewy bodies are usually in the process of dying.
4. The presence of Lewy bodies is a sign of brain aging and not necessarily of the disease.
5. Therapeutic strategies that protect neurons in model systems and enhance the formation of Lewy bodies are unlikely to succeed.

# Parkinson's disease: question 12

Parkinson's patients with recessive mutations in the Parkin gene have in most cases no Lewy bodies.

What would you conclude from this observation?

A. **(This is a different form of Parkinson's disease, with mechanisms different from the typical disease.)**

B. **α-synuclein deposition may require Parkin activity.**

C. Parkin-mediated ubiquitination of α-synuclein is required for Lewy body formation.

D. As Parkin mutations lead to early-onset juvenile Parkinsonism, Lewy bodies do not have time to develop.

# Parkinson's disease: question 13

There is ample evidence that **mitochondrial impairment** has a critical role in Parkinson's disease. Why are all neurons not equally affected by the disease? Among these statements, which ones are correct?

**A. Mitochondrial activity is important to the survival and function of neurons producing dopamine.**

B. Only the neurons that express α-synuclein are sensitive.

**C. Different types of neurons have various mitochondrial content.**

**D. Mitochondrial function is critical in neurons with long axons.**

E. Mitochondrial pathology depends on calcium signals.