Gut Model of Parkinson's Disease

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Transneuronal transmission of α-synuclein

Hypothetical scheme showing inter-neuronal transfer of protein aggregates.
Braak Hypothesis

LP: Lewy body pathology

Nat Rev Neurosci (2017) 18(2):101-113

Early Gastrointestinal (GI) symptoms in PD

A

First group: onset of symptoms related to PD diagnosis

<table>
<thead>
<tr>
<th>Symptoms present</th>
<th>Patients with symptoms, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Before PD diagnosis</td>
</tr>
<tr>
<td>Bloating</td>
<td>After PD diagnosis</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
</tbody>
</table>

B

Multiorgan α-synuclein deposits in Parkinson’s disease

Postmortem
- Stellate ganglion
- Paravertebral sympathetic ganglia
- Vagus nerve
- Epicardial plexus
- Mesenteric sympathetic ganglia
- Enteric nervous system
- Adrenal gland
- Genitourinary tract

Living patients
- Minor salivary glands
- Submandibular gland
- Stomach
- Colon
- Skin

Clinical Interventions in Aging
2016:11 1601–1608

Brain Sci. 2016, 6, 17
Gastrointestinal injection mouse models of PD

1. Holmqvist et al., 2014

<table>
<thead>
<tr>
<th>Brainstem</th>
<th>0.5d</th>
<th>2-3d</th>
<th>6d</th>
</tr>
</thead>
</table>

2. Manfredsson et al., 2018

3. Uemura et al., 2018


Neurobiology of Disease 112 (2018) 106–118


BSA
PD Lysate
Fibril

Brainstem

Vagus

Intestine

Distance from skullbase, mm

Intestine

Bregma −7.08 mm

Bregma −7.48 mm

4V

dmX

HG
2. Manfredsson et al., 2018

12 Months after colonic PFF injection

**No overt loss of nigral dopamine neurons**
Injection sites

A

\( \alpha \)-synuclein preformed fibrils (PFF)

Mean = 64.7 nm ± 1.7 nm

B

PS: Pyloric stomach; UD: Upper duodenum
p-α-Syn (LB pathology) in the gut (injection sites)

UD : Upper Duodenum; PS : Pyloric Stomach
p-a-Syn (LB pathology) in Brain

<table>
<thead>
<tr>
<th>PBS</th>
<th>PFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mon</td>
<td>10 mon</td>
</tr>
<tr>
<td>DMV nuclei</td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td></td>
</tr>
<tr>
<td>HIP</td>
<td></td>
</tr>
<tr>
<td>PFC</td>
<td></td>
</tr>
</tbody>
</table>

**DMV nuclei**

**Amygdala**

**HIP**

**PFC**

**LC nuclei**

**SNC**

**Olfactory bulb**

**Striatum**

*p-a-Syn* positive cells (p-a-Syn*/mm²)

- DMV
- LC
- AMG
- SNC
- HIP
- STR
- PFC
- OB

**Significance Levels**

- **p < 0.01**
- **p < 0.001**
- **n.s.**

**Notes**

- N.D.: Not determined
Temporal propagation of p-a-Syn (LB pathology) in Brain

Neurodegeneration in SNC

A

TH/Nissl

PBS

PFF

250 μm

SNC region of ventral midbrain

B

TH positive neurons ($\times 10^3$)

PBS

PFF

1 mon 3 mon 7 mon 10 mon

C

Nissl positive cells ($\times 10^3$)

PBS

PFF

1 mon 3 mon 7 mon 10 mon

SNC: Substantia Nigra pars Compacta
Neurodegeneration in Striatum (STR)

A

1 mon  3 mon  7 mon  10 mon
PBS  PFF  PBS  PFF  PBS  PFF  PBS  PFF

TH

100 μm

50 μm

% TH fiber density in STR

0  50  100  150
1 mon  3 mon  7 mon  10 mon

n.s  n.s  ***  ***

PBS  PFF

B

DA (ng/μg)

0  500  1000  2000
PBS  1  3  7 (mon)

n.s  *  ***

PBS  PFF

C

SPECT/CT: Single Photon Emission Computed Tomography-Computed Tomography

Coronal  Transaxial  Sagittal  MIP

Vehicle

PFF

D/A

L  R

% ID/cm³

0  0.5  1.0  1.5
Right  Left

**  **

PBS  PFF
Vagotomy and SNCA KO mice

A

Vagus nerve
Vagotomy
PFF Injection sites
Stomach

TV : Truncal Vagotomy; SNCA-/-: alpha-synuclein knockout

PBS injection in PS and UD

B

7 months PFF injection in PS and UD

TH/Nissl

WT

TV

Snca-/-

TH positive neurons (x 10^3)

0

3

6

9

12

PBS

PFF

250 µm

WT

TV

Snca-/-

***

n.s

n.s

n.s

n.s

TV : Truncal Vagotomy; SNCA-/-: alpha-synuclein knockout
Vagotomy and SNCA KO mice

A

7 months

<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th>TV</th>
<th>SNCA^{/-}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBS</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PFF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBS</td>
<td></td>
<td></td>
<td>n.s</td>
</tr>
<tr>
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<td></td>
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</tr>
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<td></td>
<td></td>
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</tr>
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</table>

B

% TH fiber density in STR

WT       TV       SNCA^{/-}

DA (ng/µg)

WT       TV       Snca^{/-}

C

Rotarod test

Latency to fall (sec)

WT       TV       Snca^{/-}

Pole test

Pole time (sec)

WT       TV       Snca^{/-}

Forelimb

Force (grams)

WT       TV       Snca^{/-}
Pole test movies
Non-motor symptoms in GI-injection mice

A, B, and C: Spatial learning and memory
Morris Water Maze movies

Spatial learning and memory
Non-motor symptoms in GI-injection mice

A: Recognition memory

![Graph showing novel object recognition test results for WT, TV, and Snca−/− mice.](image)

B: Fear memory

![Graph showing step-through passive avoidance test results for WT, TV, and Snca−/− mice.](image)

C: Short term or working memory

![Graph showing Y-maze test results for WT, TV, and Snca−/− mice.](image)
Non-motor symptoms in GI-injection mice

A, B, and C: Motor function and emotion

D, E, and F: Anxiety
Elevated Plus Maze movies

Anxiety
Non-motor symptoms in GI-injection mice

G, H, and I: Anxiety

G and H: Depressive like symptom

J and K: Depressive like symptom
Forced swimming test movies

Depressive like symptom
Non-motor symptoms in GI-injection mice

A, B, and C: Olfactory dysfunction

A: Pellet (sweetened cereal) was used in the experiment.

Mice were allowed to eat the food pellet after discovery.

B: Latency time (sec) for buried pellet trial.

C: Latency time (sec) for visible pellet trial.

Baseline: WT, TV, Snca+/

Treatment: PBS, PFF

Days: 1, 2, 3, 4
Gut-to-brain propagation of pathologic α-synuclein via the vagus nerve causes PD
Dopamine neurons degenerate in the pathologic α-synuclein gut-to-brain model of PD
Gut injection of pathologic α-synuclein causes PD-like motor and non-motor symptoms
PD-like pathology and symptoms require endogenous α-synuclein
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