

Exercise : The Gut-brain axis and its role in PD pathogenesis

Over the last two decades, scientists have proposed that Parkinson's disease (PD) might not always begin in the brain. Instead, misfolded aSynuclein (aSyn) could originate in the gut and spread to the brain along the vagus nerve, a concept known as the **gut-brain axis hypothesis**.

Holmqvist et al. (2014), *Acta Neuropathologica*

<https://link.springer.com/article/10.1007/s00401-014-1343-6>

Fig.5

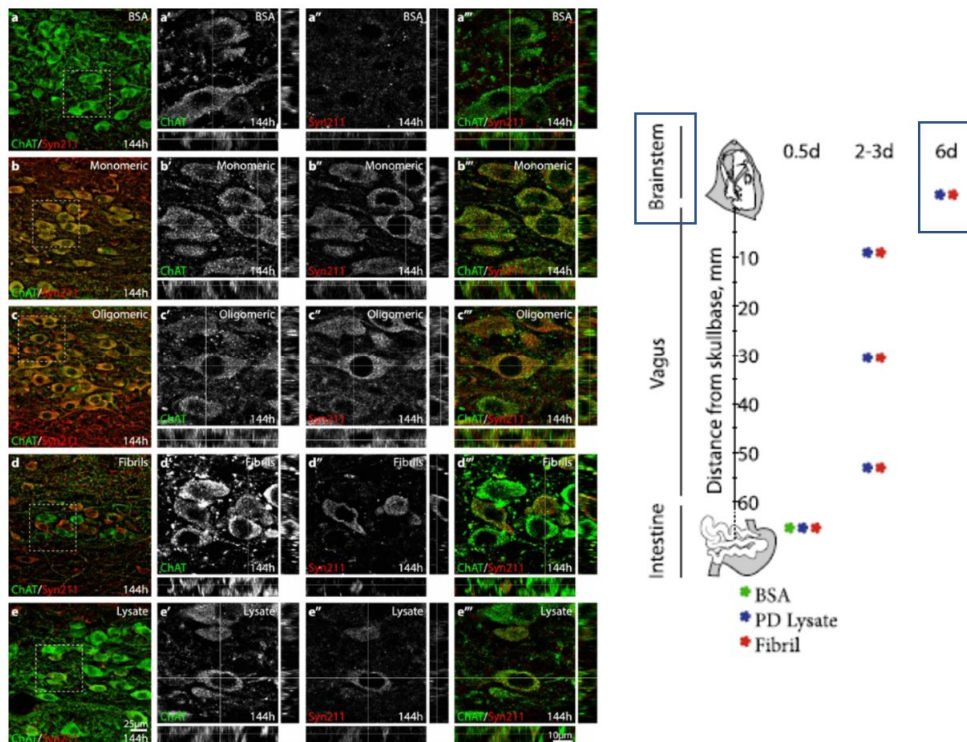


Figure. aSyn forms are specifically transported into the dorsal motor nucleus of the vagus (DMV), 144 h after injection into the wall of the intestine. To enhance the signal the brain sections were immunostained with antibodies directed specifically against human aSynuclein (Syn211, red, a-e, a''-, a'''-e''') and ChAT (green, d a-e, a'-d', a'''-e'''), the phenotypic markers of the DMV. Monomeric (b), oligomeric (c), fibrillar (d) aSynuclein and PD patient brain lysate (e) injected animals display double-labeled neurons (arrows), while BSA injection does not yield any aSynuclein-positive neurons (a''). Scale bars 25 μm in a-e, and 10 μm in a''-e'''

Questions Holmqvist et al. (2014), *Acta Neuropathologica*

1) Experimental setup

What kinds of aSynuclein species were injected into the intestinal wall of rats? What was the negative control? Why did they choose to do an immunofluorescence using human Syn211?

2) Anatomical pathway

The schematic (right side) shows signal detected at different time points and distances. What route does aSynuclein take from the intestine to the brainstem?

3) Immunofluorescence

The green signal is ChAT (a marker for vagal cholinergic neurons), and the red is human aSyn (Syn211 antibody). What does it mean when you see yellow (overlap) in these images?

4) Comparing aSyn forms

Look at monomeric, oligomeric, fibrillar aSyn, and PD brain lysates. Which forms are transported to the brainstem? Which are not?

5) Timing

How long after injection is aSyn detected in the brainstem? What does this suggest about the mode of transport?

6) Integration

In 2–3 sentences, explain why this figure is considered **direct evidence** of gut-to-brain propagation of aSyn in Parkinson's disease.

Kim et al. 2019, Neuron

<https://www.sciencedirect.com/science/article/pii/S089662731930488X?via%3Dihub>

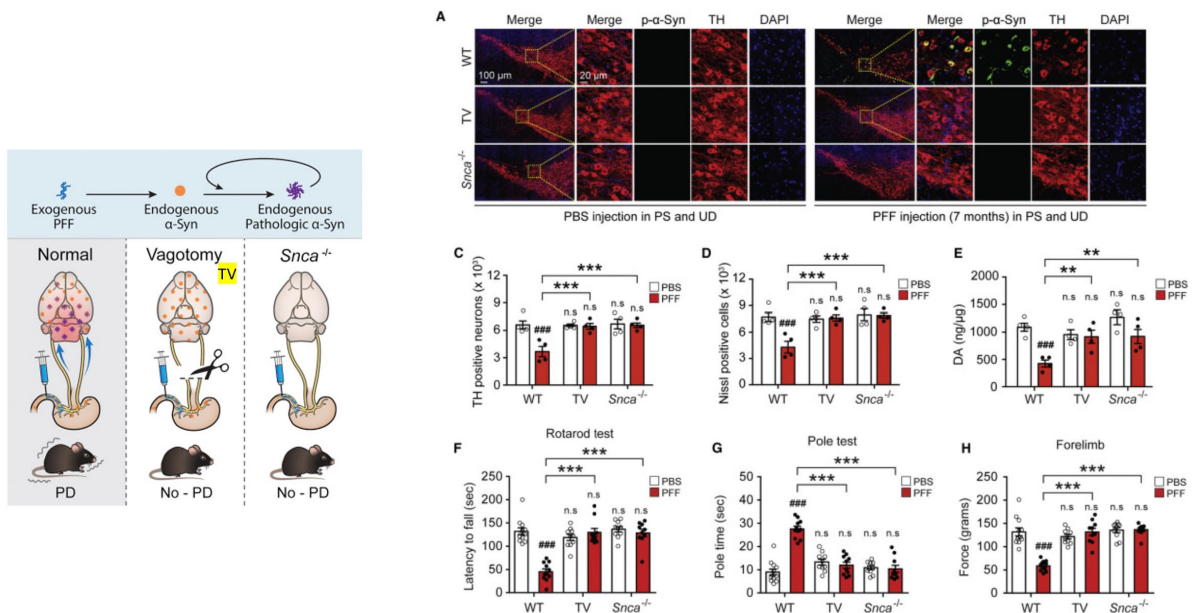


Figure 3. Vagotomy and α -syn Deficiency Prevents PD-like Pathology Induced by α -syn PFF Injection into the Gut (A) Representative double immunostaining for pSer129- α -syn (green) and TH (red) in SNc. (C and D) Stereology counts of (C) TH- and (D) Nissl-positive neurons in the SNc region of one hemisphere. Unbiased stereological counting was performed in the SNc region of WT, TV, and *Snca*^{-/-} mice (n = 4). (E) DA concentrations in the STR of PBS and α -syn PFF gastrointestinal-injected WT, vagotomy, and *Snca*^{-/-} mice as determined by HPLC (n = 4). (F–H) Behavioral assessment at 7 months after PBS and α -syn PFF gastrointestinal-injected WT (n = 11–12), TV (n = 10), and *Snca*^{-/-} mice (n = 10). Results of mice on the (F) rotarod test, (G) pole test, and (H) forelimb grip strength test are shown. Error bars represent the mean \pm SEM. Statistical significance was determined using a two-way ANOVA followed by post hoc Bonferroni test for multiple group comparison. ####p < 0.001 versus PBS gastrointestinal-injected WT group. **p < 0.01; ***p < 0.001 versus α -syn PFF gastrointestinal-injected WT mice group, n.s., not significant.

Questions Kim et al. 2019, Neuron

1) Experimental conditions

What three groups of mice were compared after injection of aSyn fibrils (PFFs) into the gut? Why are these groups informative?

2) Pathology in the brain

Look at the staining for phosphorylated aSyn (pSyn) and tyrosine hydroxylase (TH). What do you see in WT mice versus vagotomized mice versus aSyn knockout mice?

3) Neurodegeneration

The bar graphs show counts of TH+ neurons, Nissl-stained cells, and dopamine levels. What do they reveal about the effect of gut PFF injection in WT mice compared to the other groups?

4) Motor behavior

The graphs for rotarod, pole test, and forelimb use are behavioral assays. How are these results consistent with PD-like motor symptoms in WT PFF-injected mice?

5) Mechanistic requirements

Based on these results, what two factors are required for gut-to-brain aSyn pathology to produce PD-like disease? Why was including Snca^{-/-} knockout mice important?

Conclusion

Holmqvist et al. (2014) showed that pathological α -syn can move from the gut to the brainstem via the vagus. Kim et al. (2019) demonstrated that this transport leads to dopaminergic neuron loss and motor symptoms, but only if vagus and endogenous aSyn are intact.

How do these two studies together strengthen the “gut-first” hypothesis of Parkinson’s disease?

What limitations remain when translating these animal results to human PD?