

The Gut-Brain Connection and Parkinson's disease

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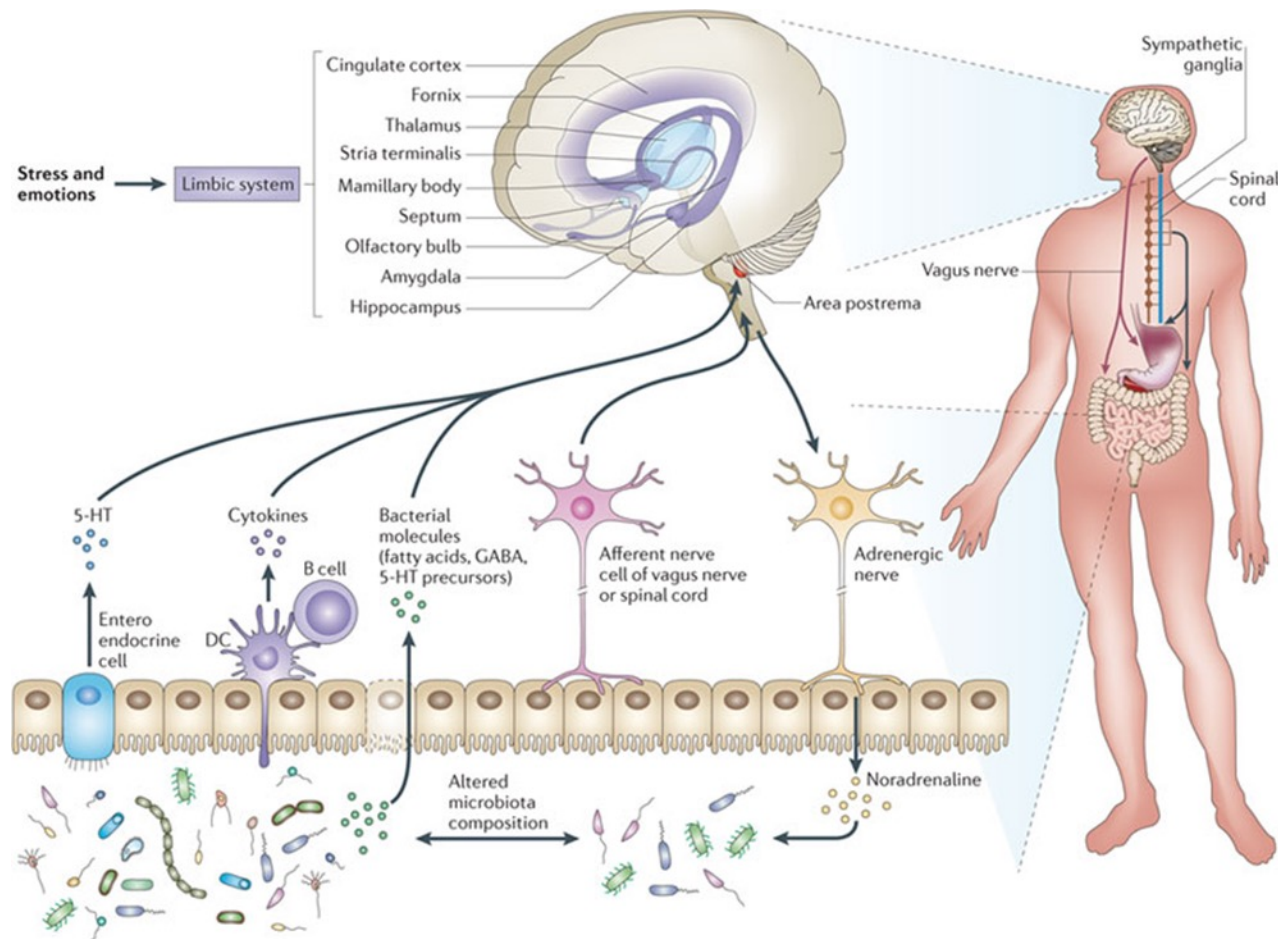
You are in the right space!
We will start at noon.

Overview of talk

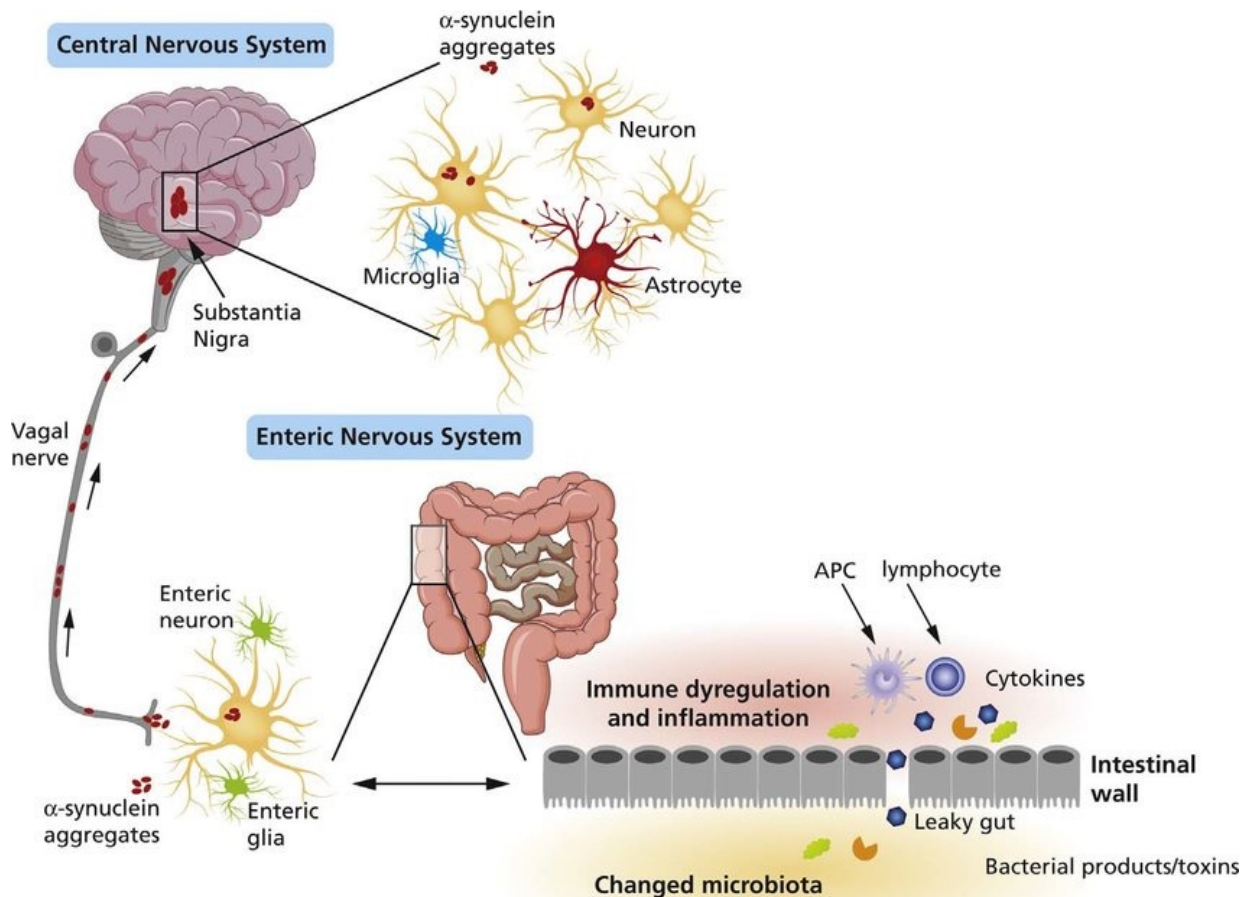
- Gut-brain connection in PD
- GI symptoms in PD
- Management of GI symptoms in PD
- Gut-related concerns in medication management
- Dietary considerations

- Alpha-synuclein: protein whose abnormal form misfolds and clumps together contributing to PD
- Microbiome: the collection of non-human cells in the body (mainly bacteria, but also viruses, fungi, parasites)
 - Gut microbiome: microbes found in the gut
- MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale

The Gut-Brain Connection




Does PD start in the gut?

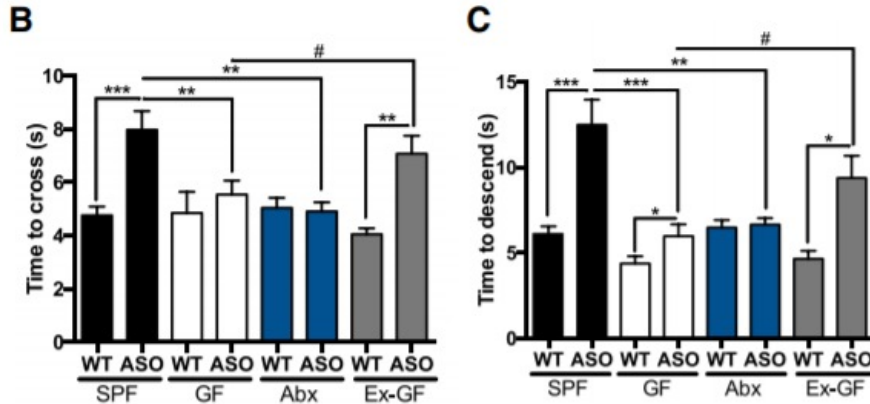


Does PD start in the gut?

- Alpha-synuclein deposits can be seen in the gut prior to development of motor symptoms of PD
- Enteric nervous system connects to the brain via the vagus
- Gut microbiome differences between PD and non-PD patients
- Gut bacteria metabolize gut contents
- The products of bacterial metabolism
 - May be involved in inflammation
 - May regulate the conversion of alpha-synuclein into disease-forming deposits
- Changes in the gut microbiome such as small intestinal bacterial overgrowth (SIBO), common in PD → “leaky gut” → systemic and/or neuro-inflammation
- Alpha-synuclein deposits may travel from the gut into the brain via the vagus nerve

- Increased
 - *Akkermansia*
 - *Lactobacillus*
 - *Bifidobacterium*
 - Reduced
 - *Prevotella*
 - *Faecalibacterium*
 - *Blautia*
 - *Lactobacillus*
- 
- Leaky Gut?
 - Increased short-chain fatty acid production
 - Inflammation
 - Increased formation of toxic alpha-synuclein types
 - Increased clumping of alpha-synuclein

Does PD start in the gut?

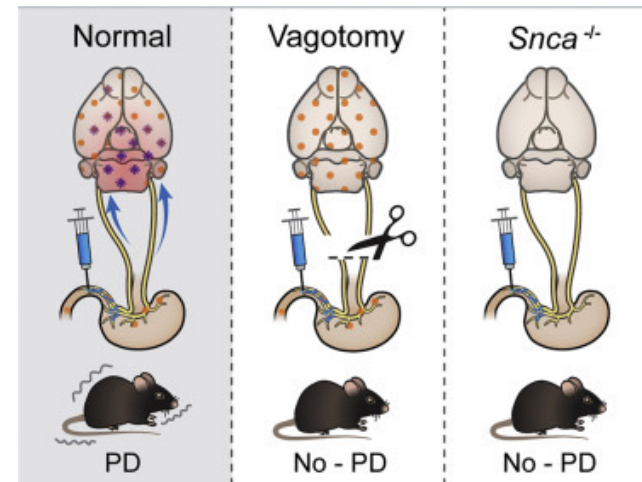


Differences noted in motor function, alpha-synuclein inclusions, microglia activation (immune system)

- Mouse model
- WT = wild-type (normal)
- ASO = genetic cause of PD (increased alpha-synuclein)
- SPF = specific pathogen-free (normal microbiome)
- GF = germ-free
- Abx = extremely high dose antibiotics (not recommended for humans!)
- Ex-GF = infused with microbiome from PD patients

Does PD start in the gut?

- Vagotomy = cutting the vagus nerve
- *Snca* ^{-/-} = mice who are missing alpha synuclein genetically
- Vagotomy in humans was associated with lower risk of subsequent PD



However...

- PD is associated with slow gut function which can alter gut microbiome
 - Chicken vs egg
- Most microbiome studies enrolled PD patients on medications which might alter the microbiome
- PD may begin in the olfactory bulb and spread to brainstem and subsequently or concurrently to gut

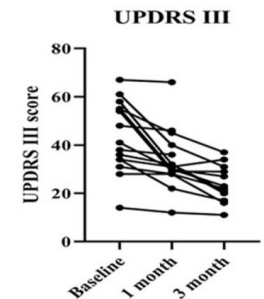
Small Intestinal Bacterial Overgrowth (SIBO)

- Found in 25% of PD patients
 - Compared to 15% of healthy older adults
- Associated with worse motor function
- Diagnosed via breath testing
 - Hydrogen
 - Methane
- Treated with specific antibiotics and temporary dietary restriction
- Do not start anti- or probiotics without guidance from an MD



Implications for PD patients

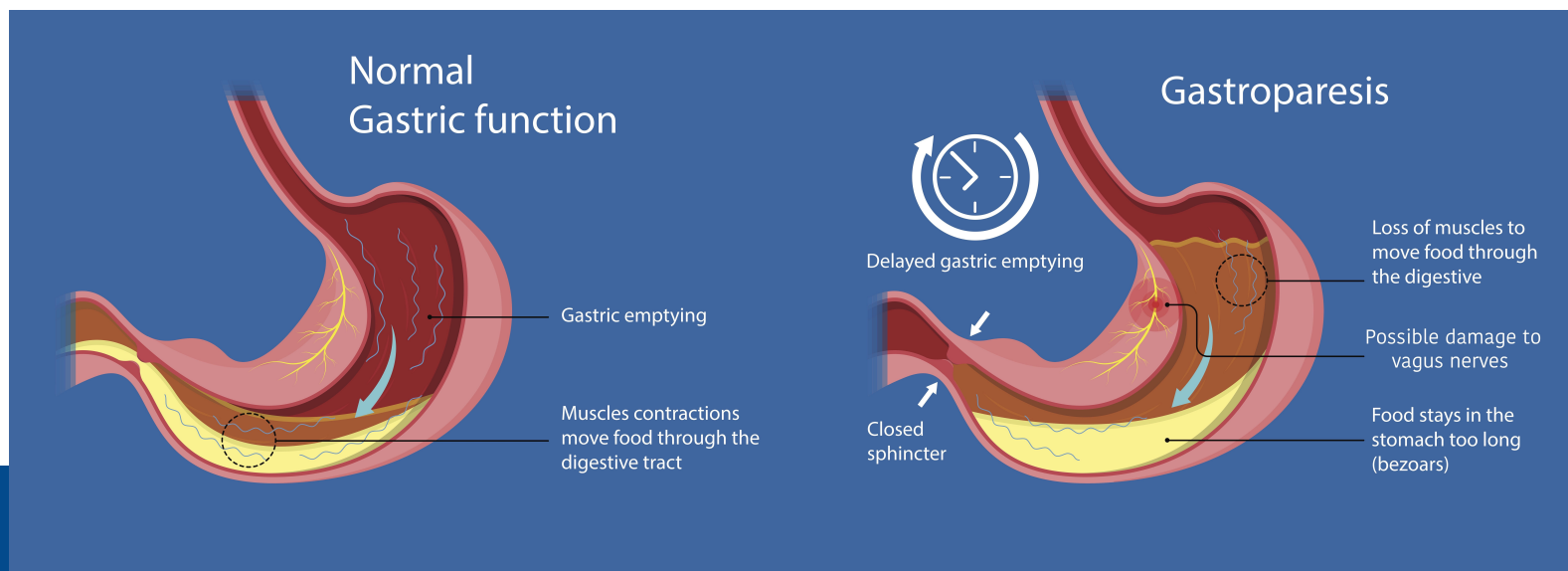
- Vagotomy?
 - high risk and very likely too late to be effective
- Probiotics?
 - Two trials showed benefit for constipation in PD
 - One RCT showed reduced total MDS-UPDRS (*L. reuteri* and *L. fermentum*)
 - Bacteria in most commercial probiotics do not survive in the gut due to stomach acid
 - Theoretical risk of inducing or worsening SIBO
 - Some probiotics contain tdc-producing bacteria
- Prebiotics (undigestible fibers that help healthy bacteria)?
 - Barley
 - Soybeans
 - Raw oats
 - Legumes
 - Onions, garlic, leeks
 - None specifically tested in PD
- Antibiotics?
 - Treatment of small intestinal bacterial overgrowth (SIBO)
- Fecal transplantation?
 - No RCT evidence yet of benefit (small open-label study showed benefit)



Xue et al., 2020

GI Symptoms in PD

- Constipation
 - Slow-transit
 - Sphincter dysfunction
- Delayed stomach emptying
 - Early satiety
 - Bloating
- Dysphagia (trouble swallowing)
- Drooling (due to reduced frequency of swallowing)
- Low appetite



Evaluation of GI Symptoms in PD

- GI evaluation may include
 - Swallow evaluation
 - Endoscopy/colonoscopy
 - Colon transit time
 - Gastric emptying study
- Consultation with a registered dietitian

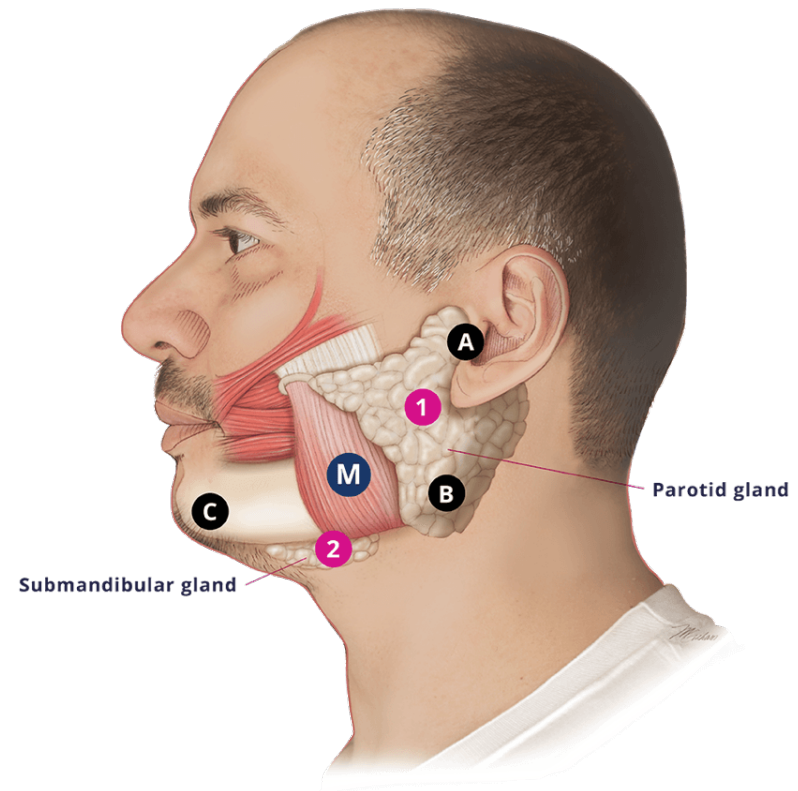


Management of GI Symptoms in PD

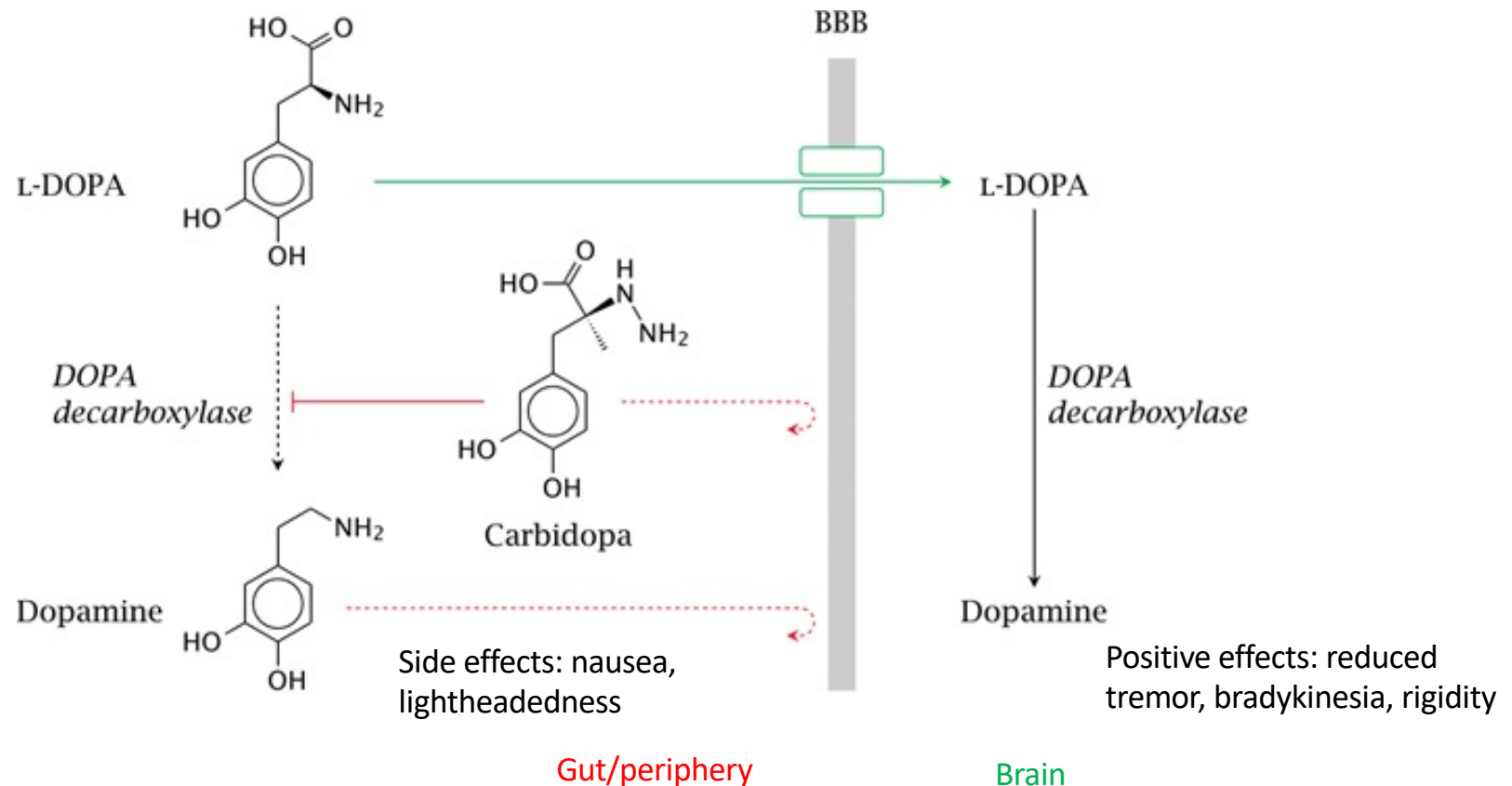
- Management of swallowing issues
 - Dysphagia diet depending on testing e.g., Pureed foods/ thickened liquids
 - Small bites and sips
 - Alternate liquids and solids
 - Preventive clear / swallow
 - Eat only upright, chew slowly
 - Avoid high risk foods such as whole nuts, dry crackers, pretzels, tough meats
- Management of constipation:
 - Colace (docusate) 100 mg twice a day.
 - Miralax 17 gram (one capful) in 4-8 oz of liquid daily or every other day
 - Dulcolax as needed
 - Fiber:
 - Soluble can reduce cholesterol and blood glucose and forms a gel; helps w/digestion
 - Insoluble: best for constipation
 - Psyllium = combination of soluble & insoluble fiber, not highly fermented
 - Inulin/Dextrin = fermented insoluble fiber, not useful for constipation
 - Water!
 - Exercise!
- Prescription strength gut motility medications
 - Linzess, Amitiza

Management of GI Symptoms in PD

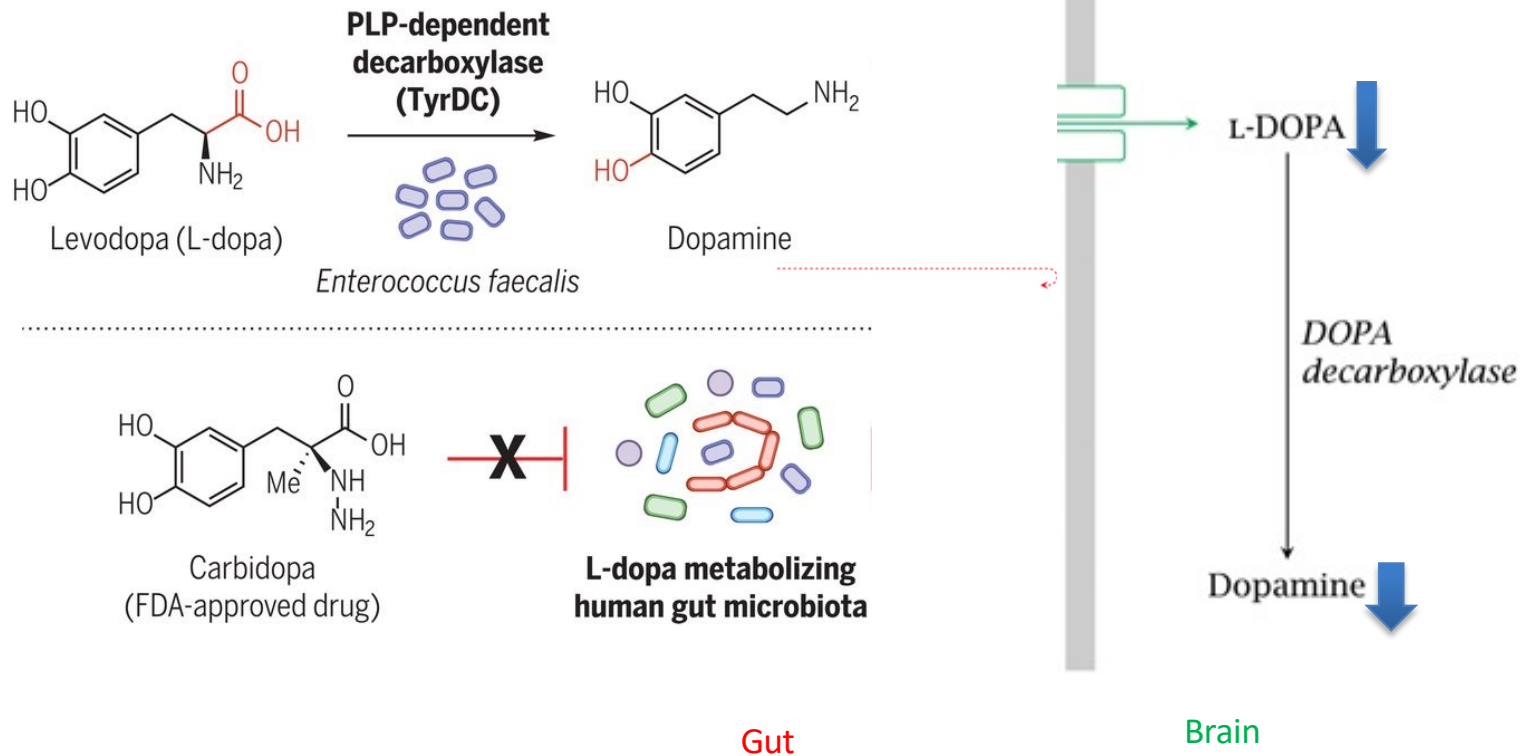
- Treatment of delayed gastric emptying
 - Blenderized foods
 - Domperidone*
 - Erythromycin
 - NO metoclopramide (exacerbates PD symptoms)
- Treatment of drooling
 - Botulinum toxin (e.g., Xeomin) injection to salivary glands



Gut bacteria inhibits levodopa action



Gut bacteria inhibits levodopa action

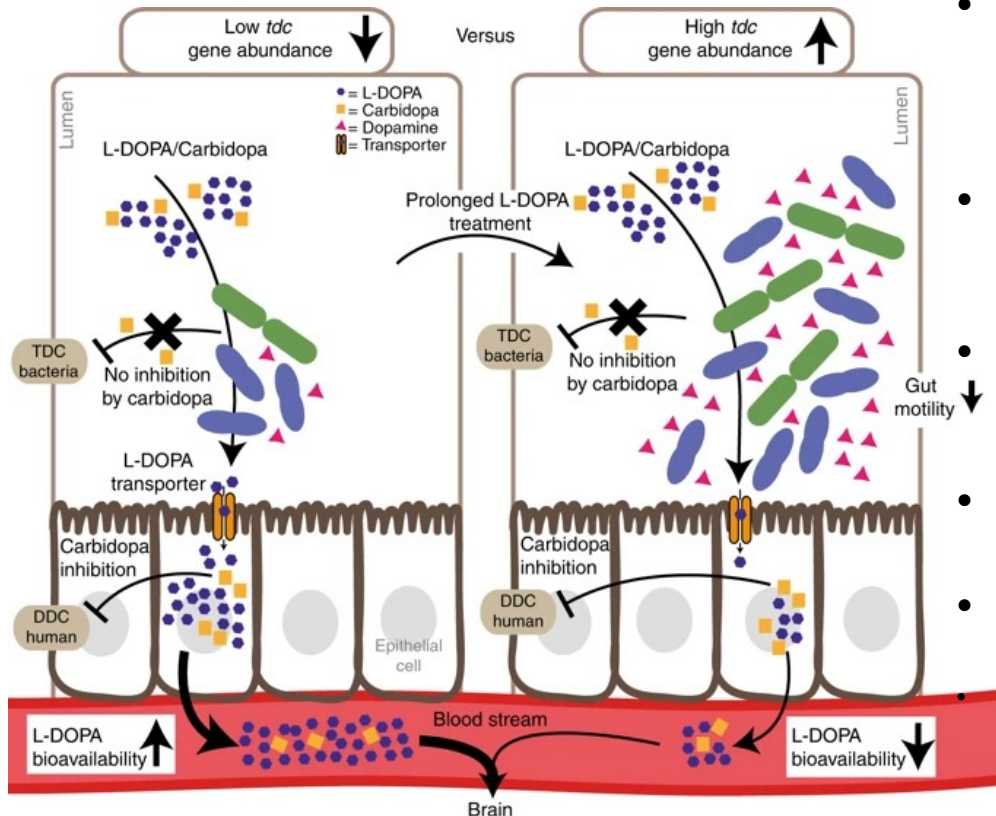


- Maini Rekdal et al., Science 2019

What affects levodopa metabolism?

- Levels of specific bacteria:
 - *Enterococcus faecalis* and *Eggerthella lenta*
- Levels of specific enzymes:
 - tyrosine decarboxylase from *E. faecalis*
- Specific SNPs (gene variant) from *E. lenta* gene that codes for a specific enzyme (dopamine decarboxylase, *dadh*)
- Maini Rekdal et al., Science 2019

Prolonged use of levodopa and disease duration are associated with increased *tdc* gene-carrying bacteria

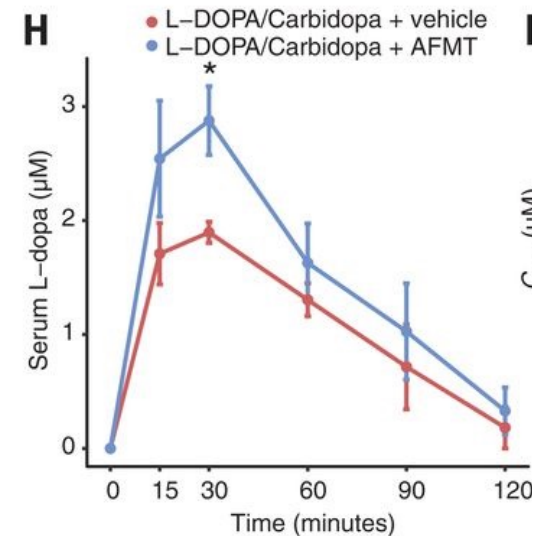


- Altered levels of gut dopamine → Impaired GI motility → SIBO → worsening of motor fluctuations → higher doses → vicious cycle
- In small intestinal bacterial overgrowth (SIBO) associated with PPI use, *Enterococcus* tends to dominate
- Prolonged use of levodopa appears to favor growth of *tdc* bacteria, further lowering efficacy of levodopa
- May identify biomarker for proper levodopa dose
- Some Probiotics contain *tdc* gene-carrying *Enterococcus*

Van Kessel et al., Nature Communications 2019

Carbidopa does not block bacterial metabolism

- Carbidopa blocks human peripheral decarboxylase enzyme
 - Making levodopa more present in serum and thus brain
 - BUT NOT BACTERIAL decarboxylase!
- Alpha-fluoromethyl-tyrosine (AFMT), an amino acid, can block bacterial tyrosine decarboxylase
 - Making levodopa more avail in mice serum
 - potential rx for managing motor fluctuations
- Maini Rekdal et al., Science 2019



What does this mean for PD patients?

- As GI symptoms progress, the gut can slow down, impacting onset of action of levodopa
- Typically levodopa should be taken on an empty stomach as protein in the gut can interfere with the absorption of levodopa
 - Med should be taken at least 30-60 minutes prior to having a meal
 - If a meal will be skipped the medication should still be taken on time
 - Med can also be taken 60 minutes after finishing a meal
- Constipation should be treated aggressively

Helpful Hints for Medication Consistency

- Taking medications on an empty stomach
- Taking medications at consistent times every day
- Preventing fluctuations of dopamine levels in the brain
 - Reduce risk of developing dyskinesias
 - Reduce risk of ON/OFF fluctuations
- Medication sets
 - Fill once a week
 - Help to verify that pills have or have not been taken but do not remind patients
- Medication alarms
 - Available as a watch or on a smart phone
 - Will not verify that the med has been taken if patient silents an alert without taking the medication.
- MedReady
 - Alerts a family member or caregiver when medications have not been taken within a certain amount of time.



Dietary Choices in PD

- MIND diet: Mediterranean Intervention for Neurodegenerative Delay

- Other considerations:

– Dysphagia

– Gastrointestinal Issues

– Delayed Gastric Emptying

– Neurogenic Orthostatic Hypotension

– Religious or other dietary restrictions

- Do your best!

– Don't let perfect be the enemy of good.

