Unveiling the Role of Gut Bacteria in Drug Transformation: Insights from Parkinson's Treatment

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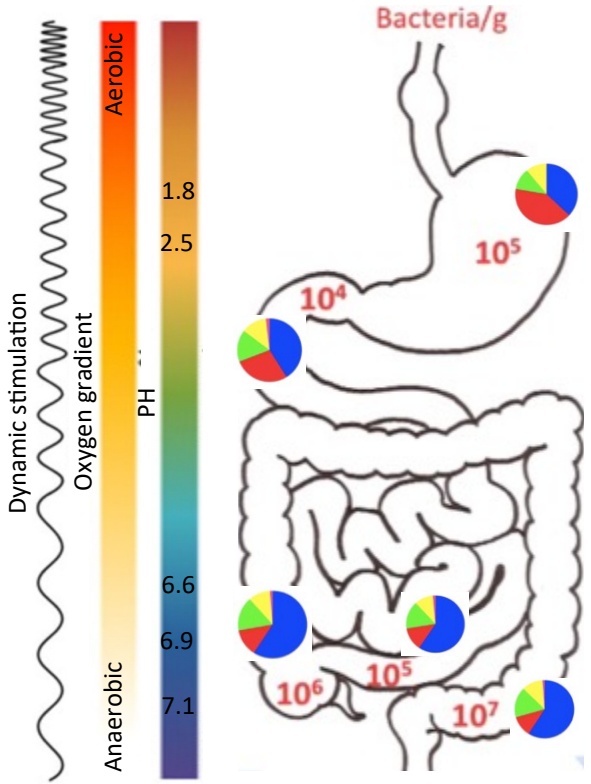
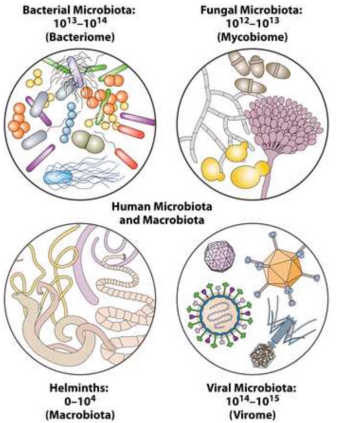
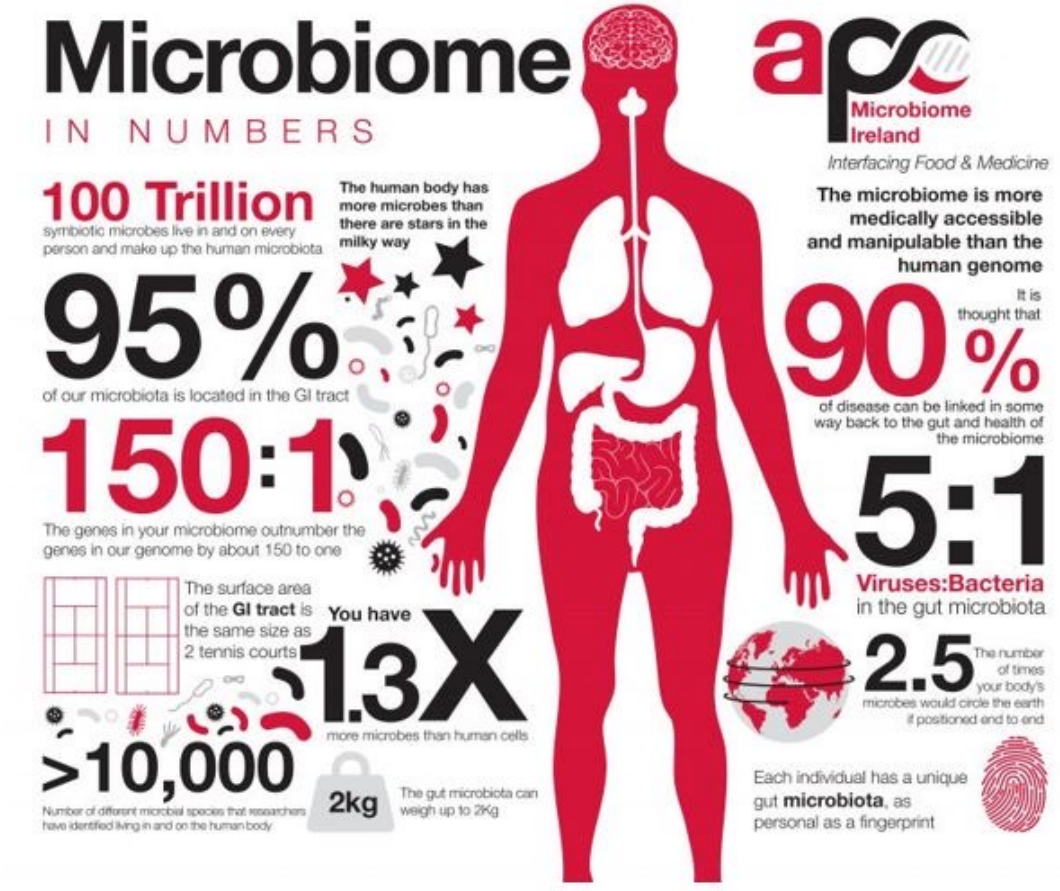
The Human Microbiota



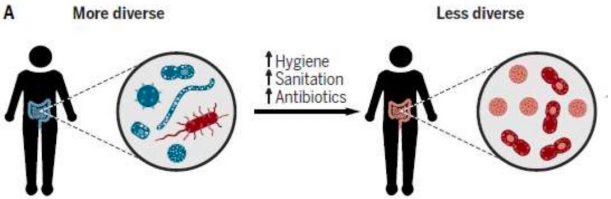


Adapted after Mailha et al., 2018, Sardille et al., 2021

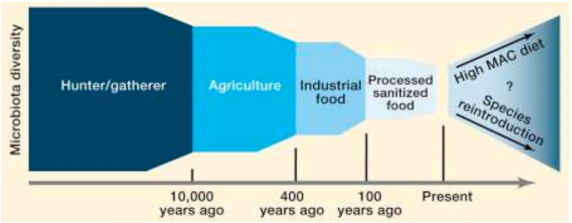
Why is it important to know the human microbiota?



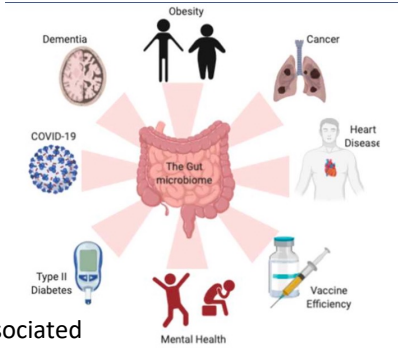
Changes in the life-style, endangered microbiota and appearance of chronic diseases



Gut microbial diversity has been reduced to 1/3 over the past decades



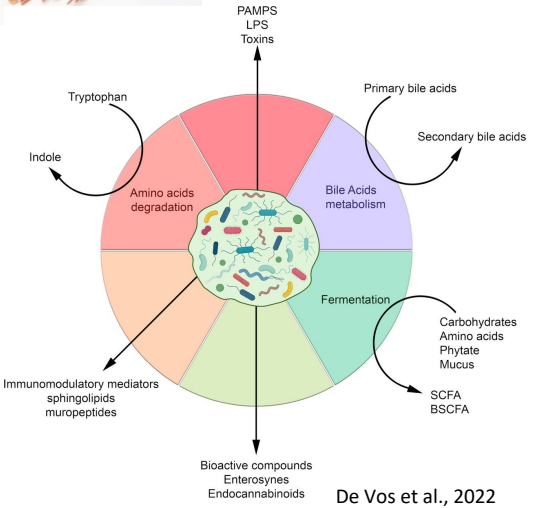
Dramatic changes in the diet during human evolution



Alteration in the gut microbiota has been associated with intestinal and extra-intestinal diseases

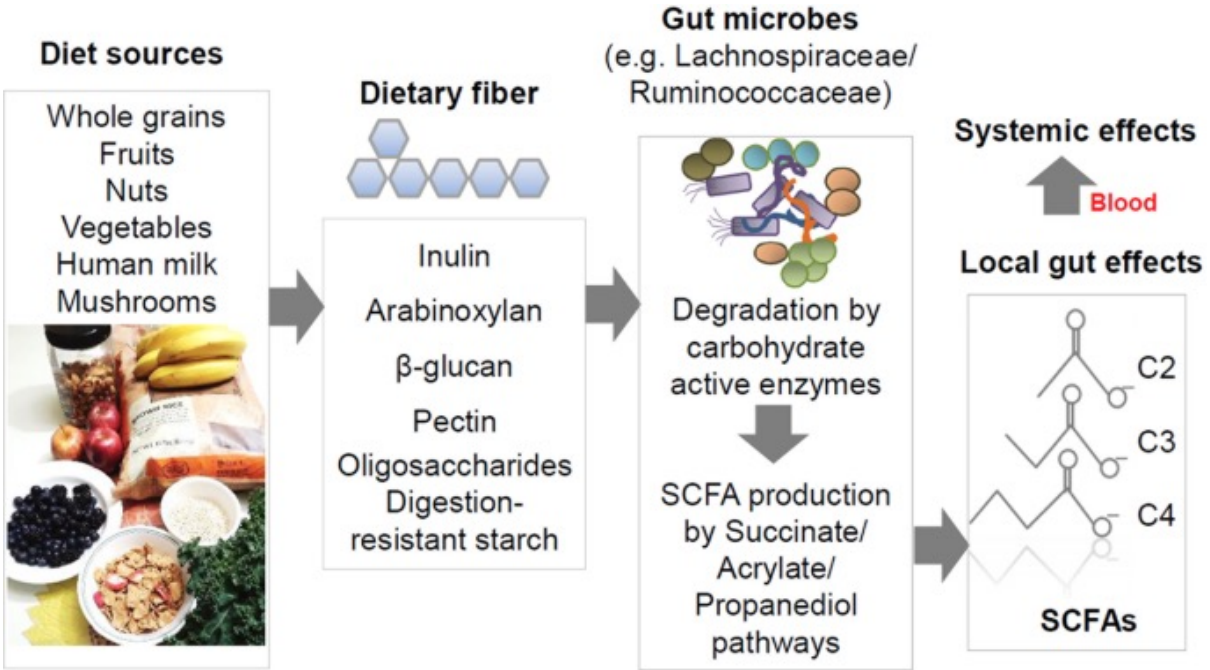
Sonnenburg and Sonnenburg, 2019; Zmora et al., 2019

Gut bacteria influence the nutritional content of our food in ways that are not understood



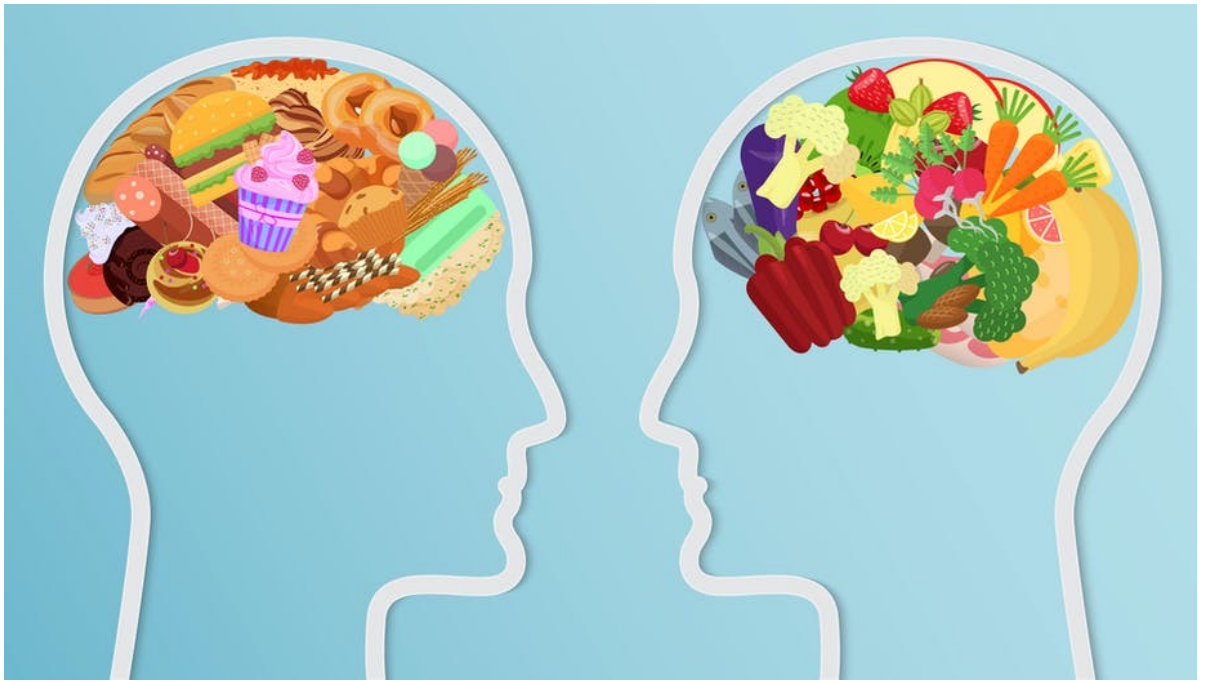
De Vos et al., 2022

How to feed your gut microbiota?



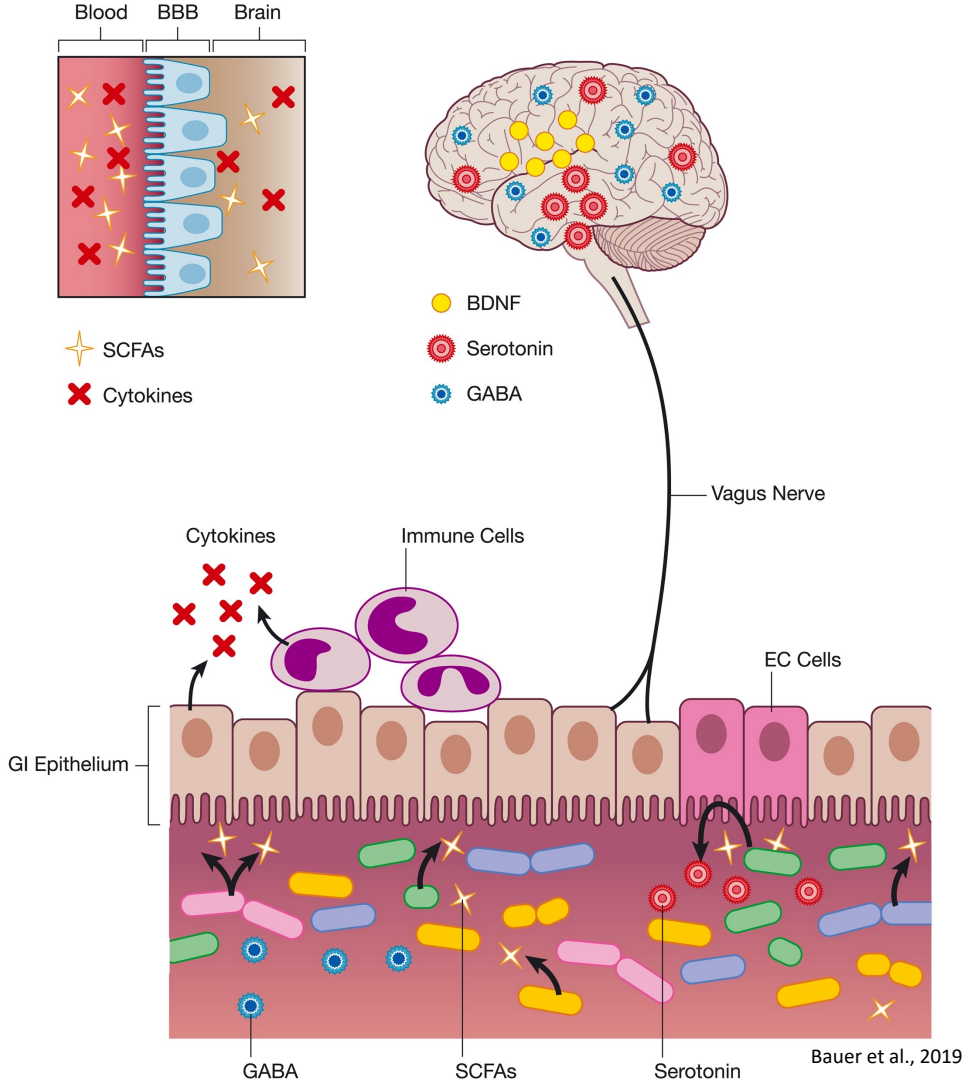
Kim, 2021

Your gut microbes play a key part in food craving, influencing your brain ?!



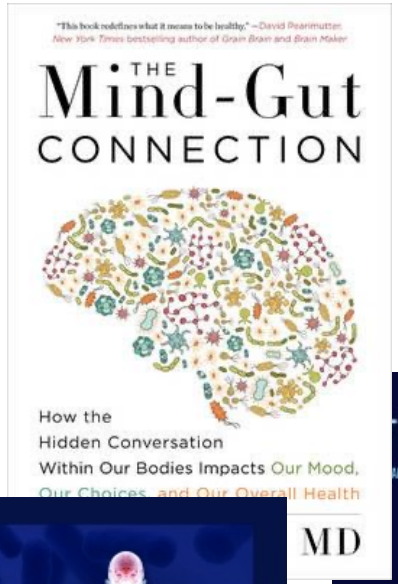
https://www.gutxy.com/blog/

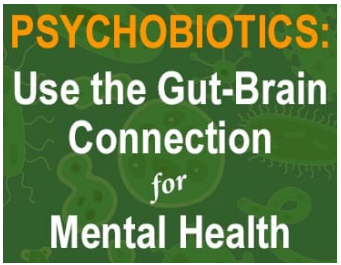
That Gut Feeling !

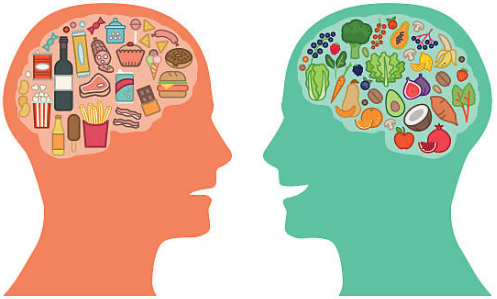


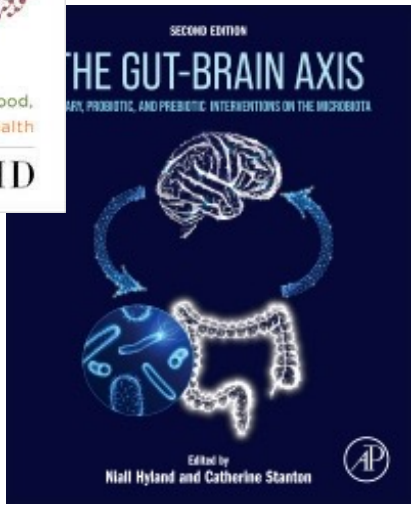
Bauer et al., 2019

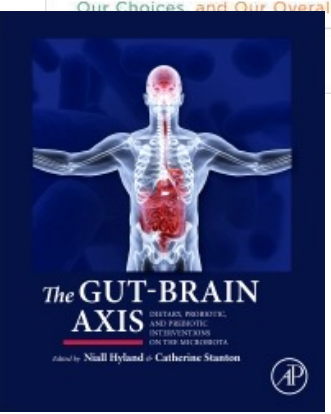
The Microbiota–Gut–Brain Axis: Hype or Revolution?

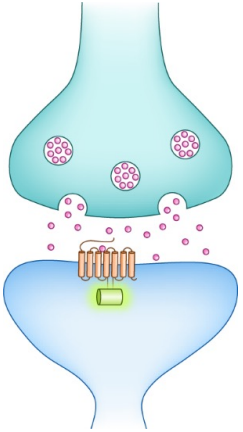




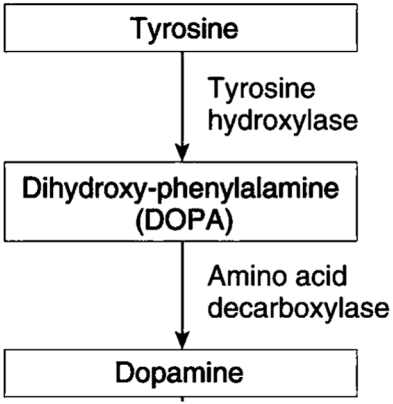


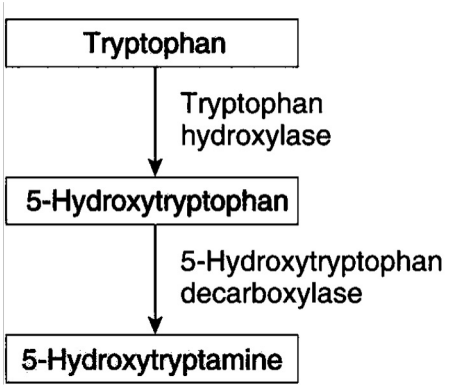




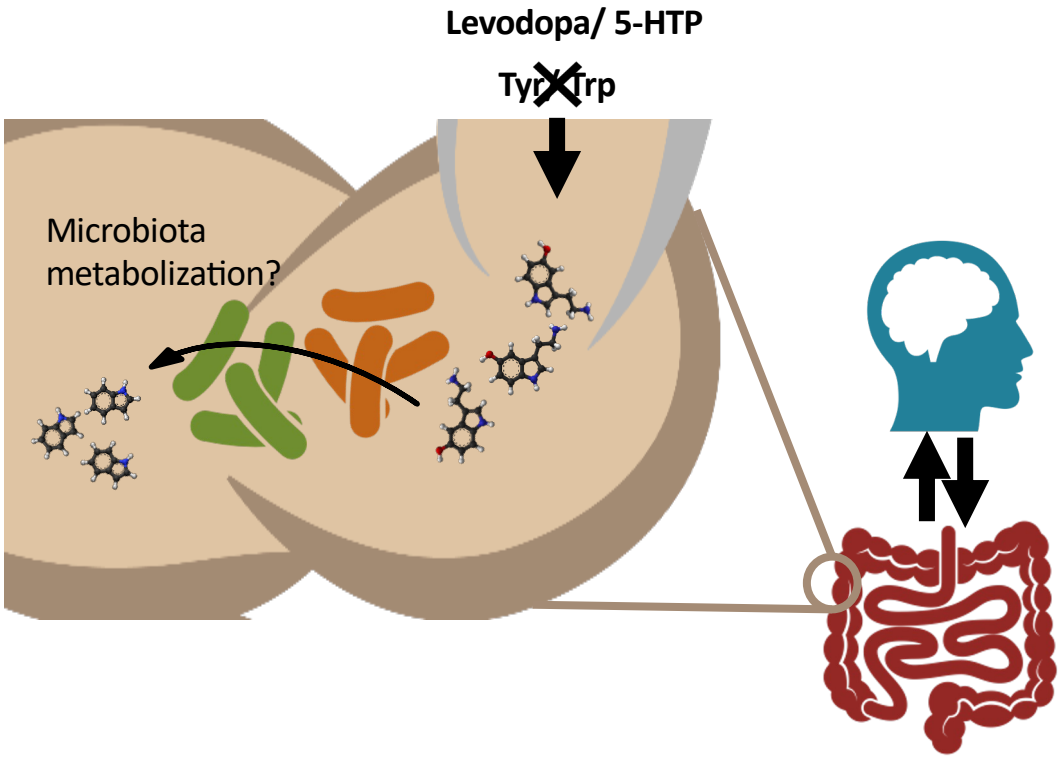


Gut Bacteria and Neurotransmitters: Verifying Production Claims

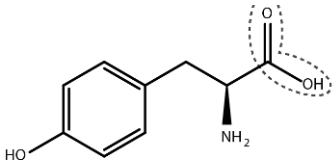




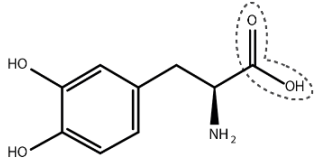
Host-Microbiome Metabolic Interactions



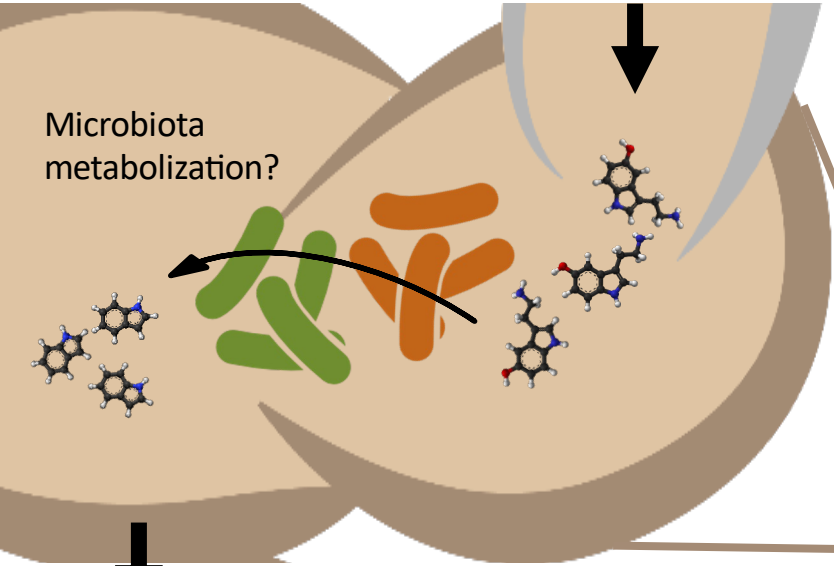
Host-Microbiome Metabolic Interactions

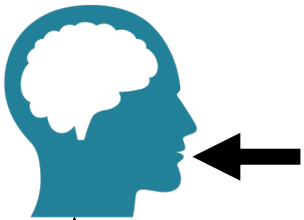


Tyrosine



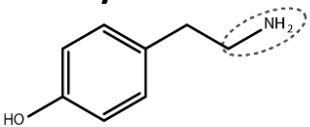
Levodopa



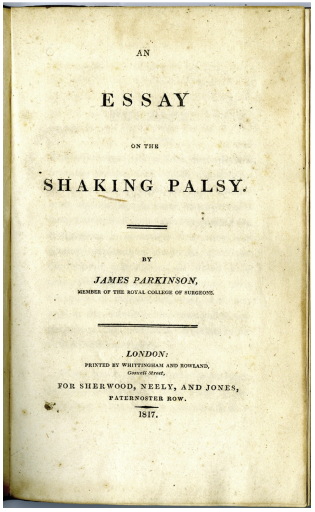


Tyrosine
Levodopa

Tyramine



Parkinson's Disease



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

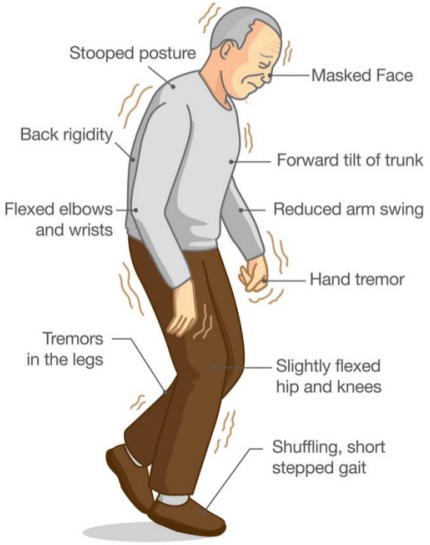
Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

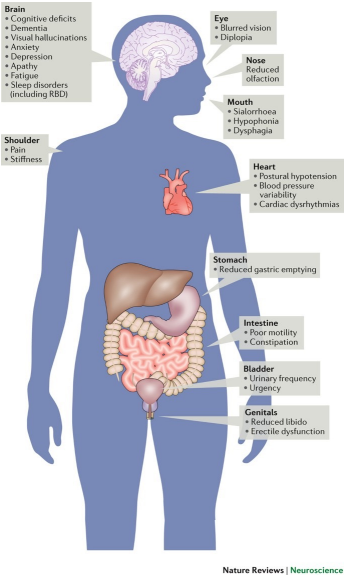
PATERNOSTER ROW.

1817.

"Shaking palsy", 1817.

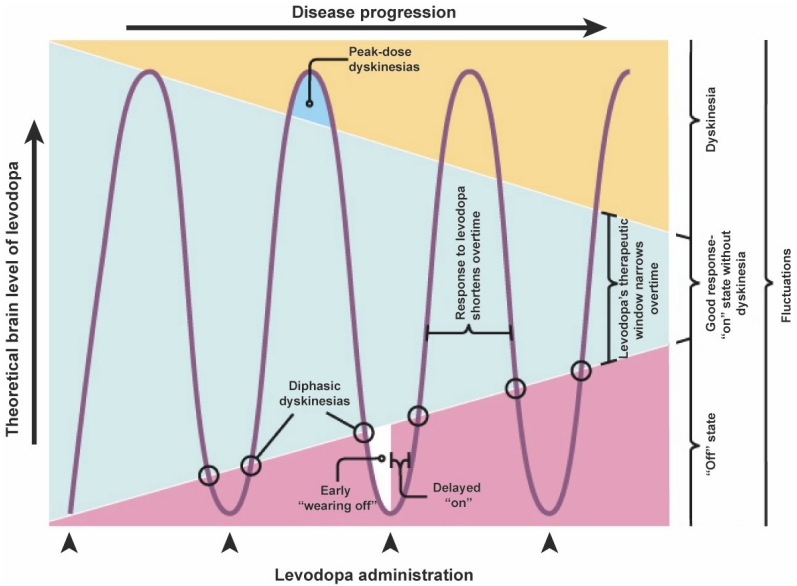


Motor symptoms
Brain-to-Body



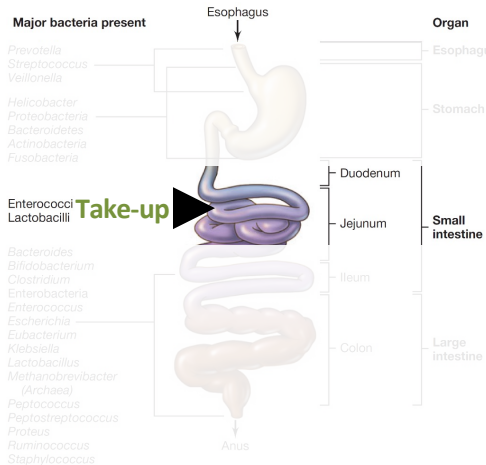
Non-motor symptoms
Body-to-Brain

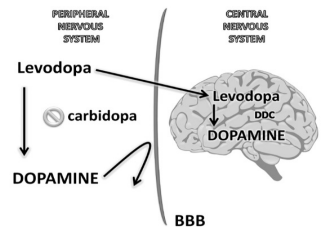
Parkinson's Disease Treatment



Therapeutic window of levodopa

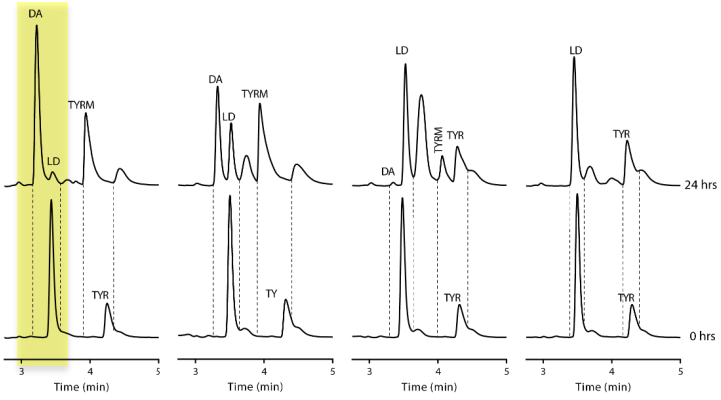
Treatment

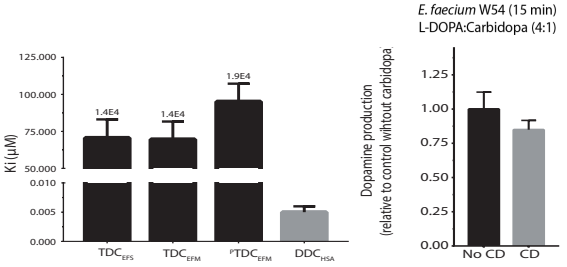




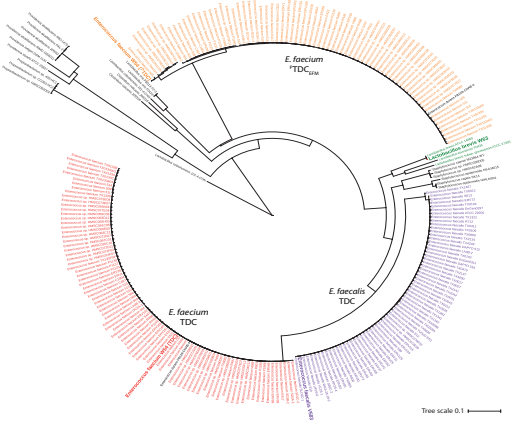
Madigan, M. T., et al.(2010). *Brock Biology of Microorganisms 13th edition*. Benjamin Cummings.

Levodopa Conversion-I: Decarboxylation by Small Intestinal Bacteria

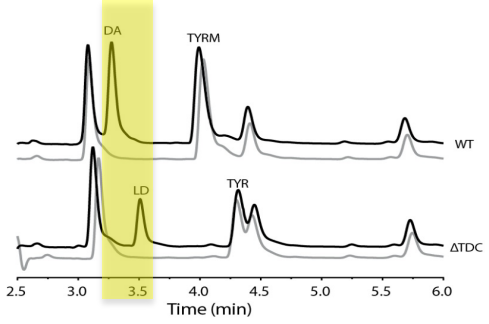




Bacilli are 1[ry] class harboring *tdc* genes in the human gut



***E. faecalis* v583**
WT vs ΔTDC

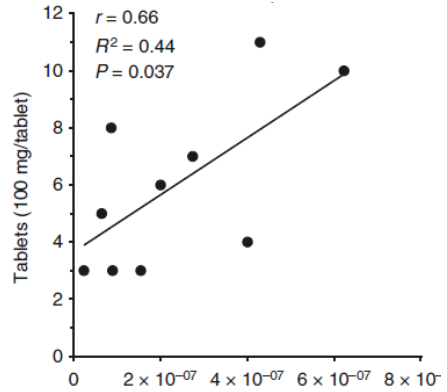


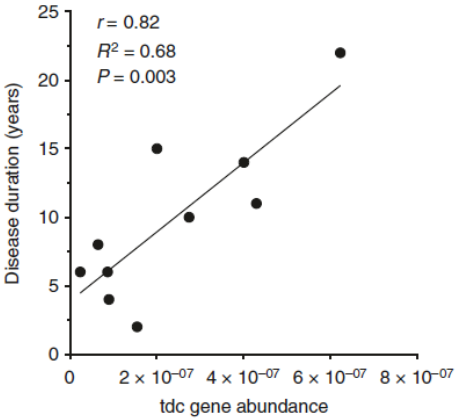
van Kessel S., et al. Nat Comm., 10 (1), 310, 2019

Parkinson's Disease Patients Vary in Dosage Regimen Requirement

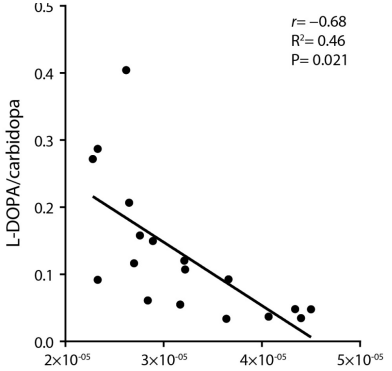
Possible Impact of Small Intestinal Microbiota?

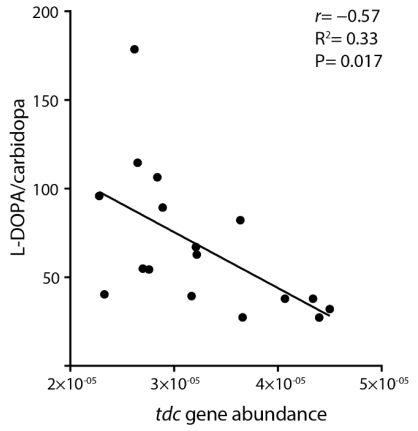
Fecal samples

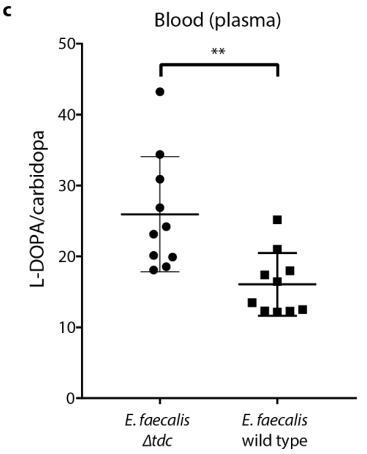




In vivo using WTG rats



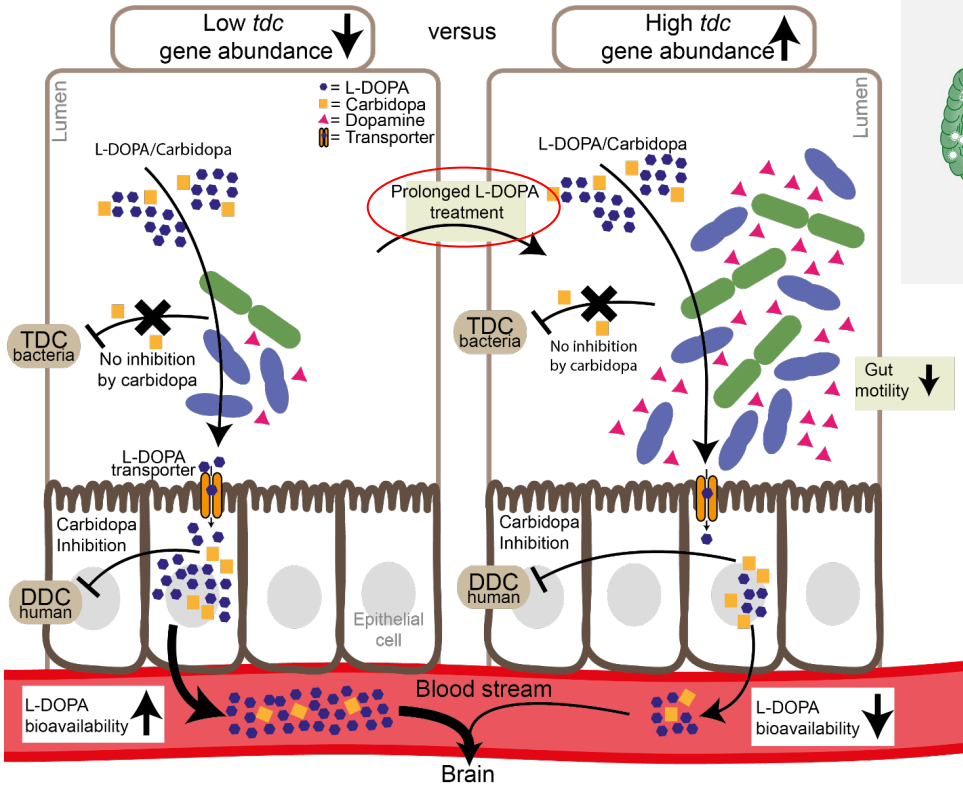


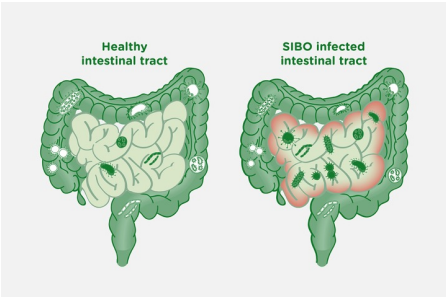


blood (plasma)
L-DOPA ↓
tdc-gene ↑

van Kessel S., et al. Nat Comm., 10 (1), 310, 2019

Small Intestinal Microbiota:
A Key Factor in Levodopa Treatment for Parkinson's Disease





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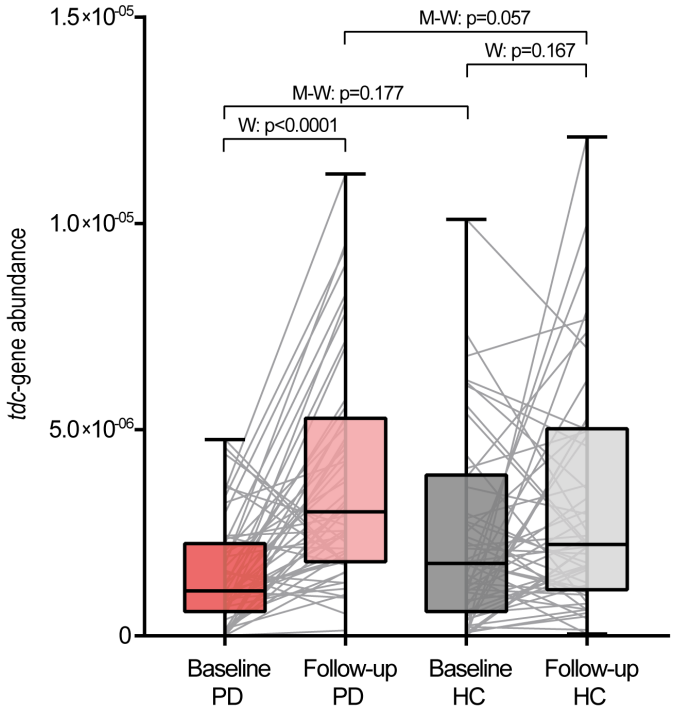
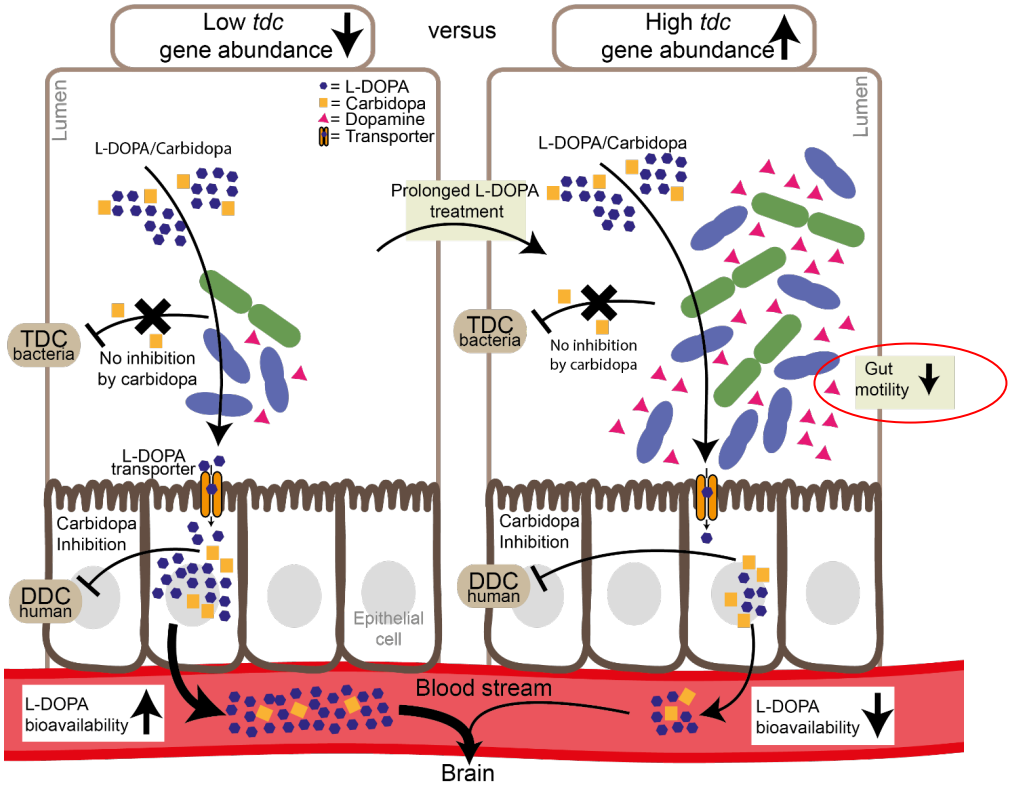
Tdc-Gene Abundance Increases Over Time in Parkinson's Disease Patients



van Kessel S., et al. NPJ Parkinson's disease 7 (1), 1-8, 2021

Small Intestinal Microbiota: A Key Factor in Levodopa Treatment for Parkinson's Disease



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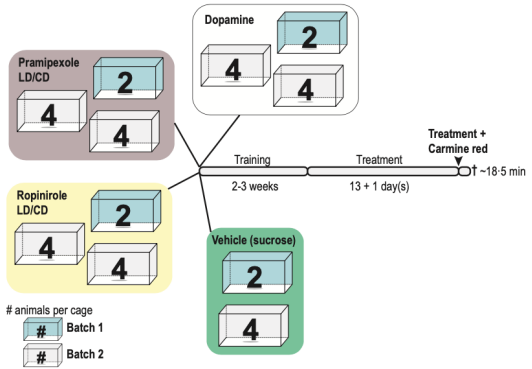
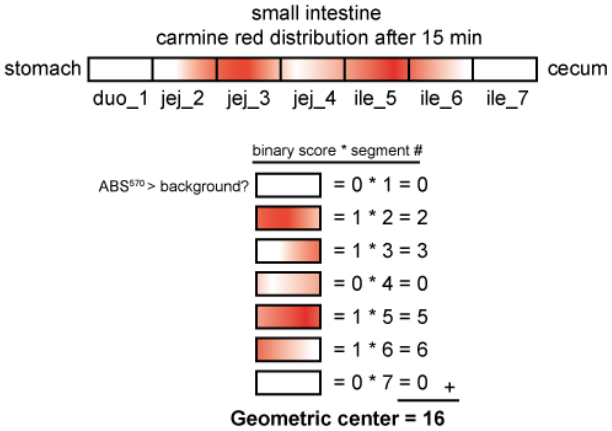
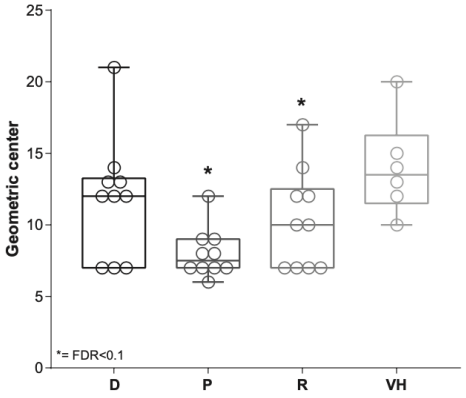
Parkinson's Disease Medication Alters Small Intestinal Motility in Healthy Rats







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Small Intestine Bacterial Overgrowth in the Healthy Rats Treated with Parkinson's Disease Medication

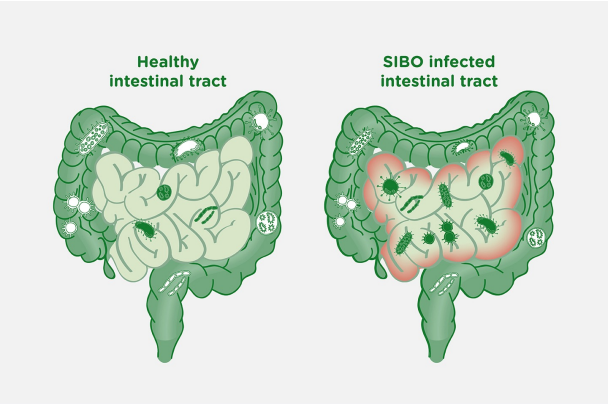
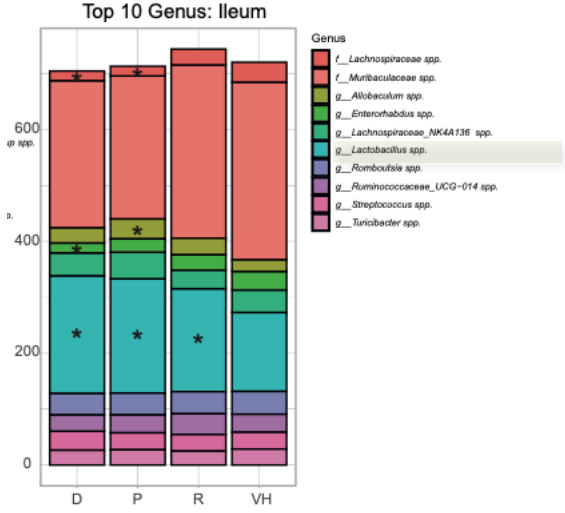


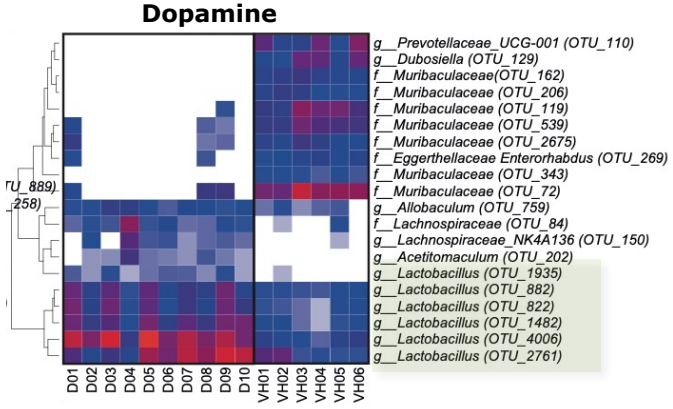
Table 1 - Bacterial counts from rat small intestine

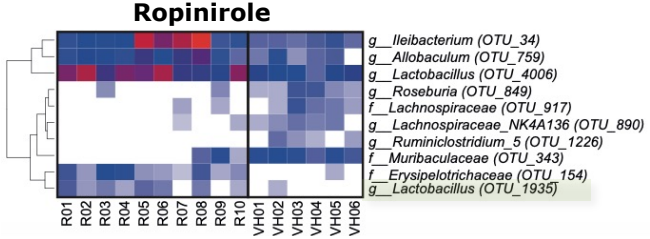
	Aerobic (CFU/mL, median (IQR))		Anaerobic (CFU/mL, median (IQR))	
	Jejunum	Ileum	Jejunum	Ileum
D	1.7E+7 (3.1E+6 – 1.5E+6)	3.6E+7 (2.5E+7 – 4.2E+6)	4.2E+7 (1.6E+7 – 2.3E+6)	5.9E+7 (4.1E+7 – 1.4E+7)
P	2.4E+7 (1.5E+7 – 2.2E+6)	5.6E+7 (2.5E+7 – 1.4E+7)	6.2E+7 (3.8E+7 – 4.6E+6)	**3.4E+8 (6.8E+7 – 2.1E+7)#**
R	1.0E+7 (4.6E+6 – 1.3E+6)	**1.8E+8 (7.5E+7 – 3.6E+7)***	2.7E+7 (1.0E+7 – 3.9E+6)	**2.8E+8 (1.2E+8 – 4.4E+7)***
VH	3.5E+7 (9.5E+6 – 2.6E+6)	2.4E+7 (2.1E+7 – 7.0E+6)	6.9E+7 (2.8E+7 – 3.8E+6)	7.0E+7 (4.8E+7 – 3.4E+7)

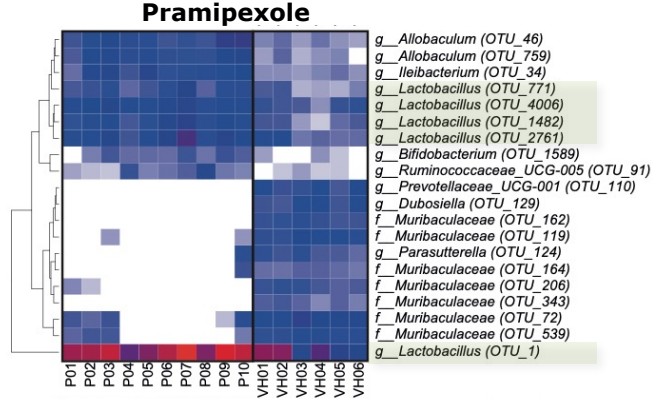
van Kessel S., et al. mSystems 7 (1), e01191-21, 2022

Dopamine Agonists Increase *Lactobacillus* abundance in the Small Intestine of Healthy Rats









van Kessel S., et al. mSystems 7 (1), e01191-21, 2022

Microbiota imbalance in Parkinson's disease Patients

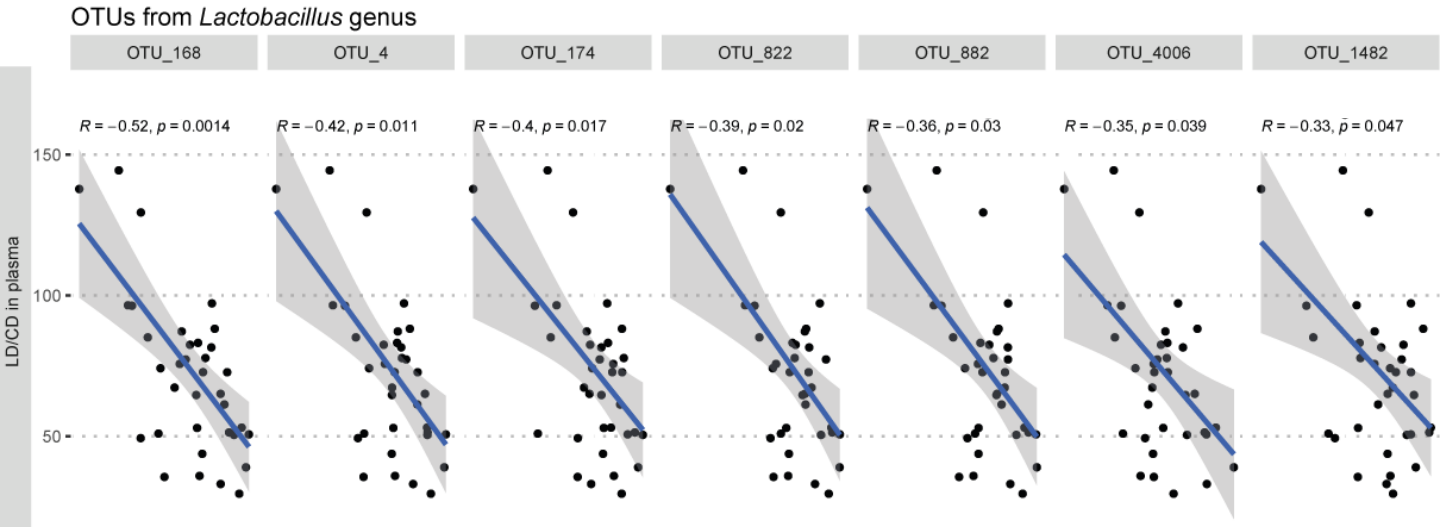
Comparing 13 different studies:

- 54% (7/13) of the studies report an **increase** of *Lactobacillaceae* or *Lactobacillus*

Which are associated with increase in tyramine (or downstream metabolites) and important as they could potentially contribute to decarboxylation of levodopa.

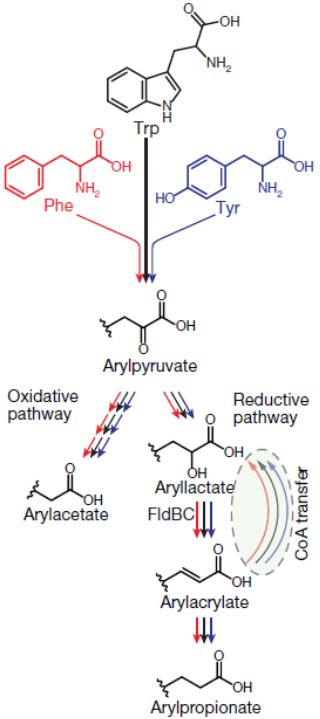
van Kessel & El Aidy, J. of Parkinson's Disease, 9(2), S359-S370, 2019

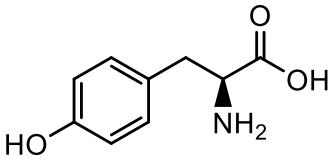
Lactobacillus taxa Linked to Lower Levodopa Levels in Blood samples of Healthy Rats



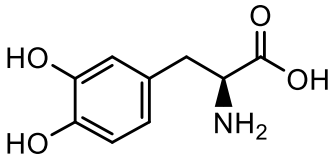
van Kessel S.,. mSystems 7 (1), e01191-21, 2022

When Gut Bacteria Encounter Unabsorbed Levodopa Residues…

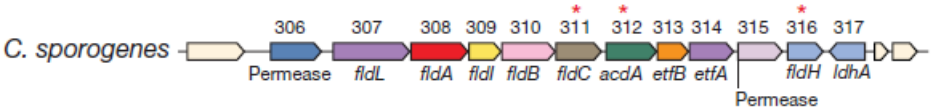




L-tyrosine



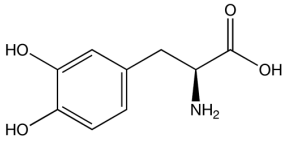
L-DOPA



Anaerobic aromatic amino acid deaminase pathway in *C. sporogenes*

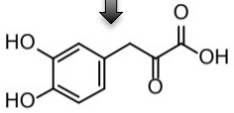
Dodd et al. *Nature* 2017 Nov

Levodopa Conversion-II: deamination by Colonic Bacteria



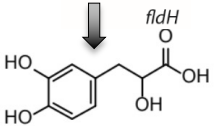
Levodopa

Unidentified transaminase



3-(3,4 dihydroxyphenyl)pyruvic acid

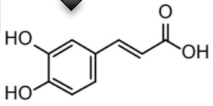
fldH



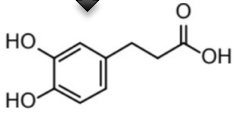
3-(3,4 dihydroxyphenyl)lactic acid (DHPLA)

L.l.LtrB-ery^R*ΩfldC* disrupted dehydratase

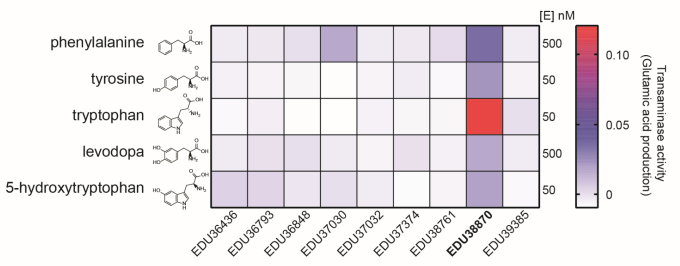
fldBC



3-(3,4 dihydroxyphenyl)acrylic acid



3-(3,4 dihydroxyphenyl)propionic acid (DHPPA=dihydrocaffeic acid)

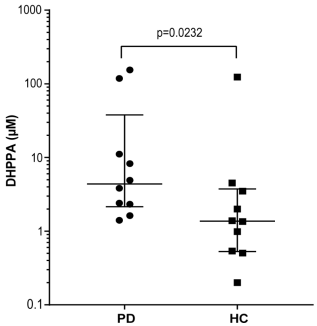


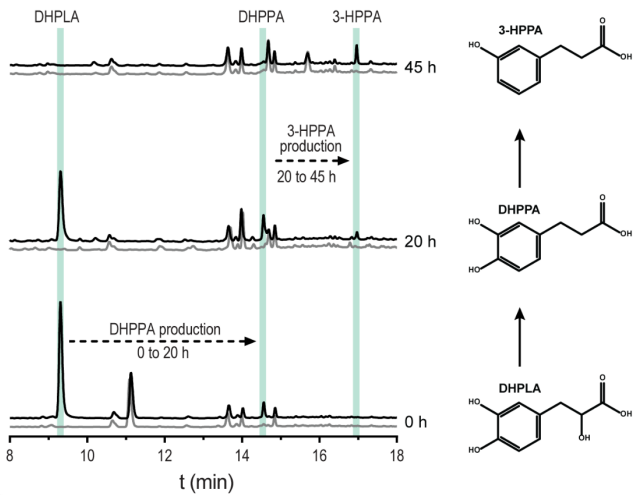
C. sporogenes class II aromatic aminotransferases

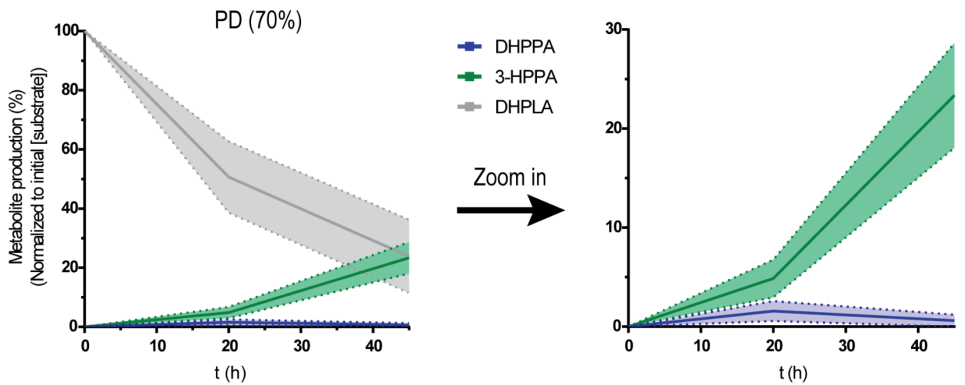
Uncovering of the first step in anaerobic deamination: AAA transaminase

van Kessel S., et al., BMC Biol. (2020) 18:137.

Higher levels of levodopa deamination products in Parkinson's Disease patients







van Kessel S., et al., BMC Biol. (2020) 18:137.

Implications of Levodopa deamination Metabolites on Parkinson's Disease Patients

Table 1. Prevalence of gastrointestinal symptoms in patients with Parkinson's disease affected by SIBO versus those without SIBO

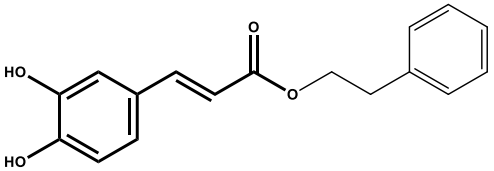
	SIBO positive, % (n = 26)	SIBO negative, % (n = 22)	OR (CI)
Abdominal discomfort	30.8	27.3	ns
Bloating	69.2	31.8	2.07 (1.42–16.40)
Flatulence	65.4	36.4	1.74 (1.01–10.83)
Constipation	73.1	81.8	ns
Diarrhea	19.2	9.1	ns

Gabrielli et al. *Movement Disorders*, Vol. 26, No. 5, 2011

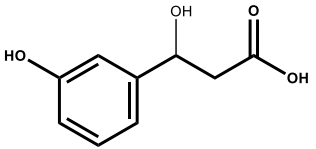
Test the effect on gut transit time in animal models

Affected gut contractibility in rat intestine

Aviello et al. *Eur J Pharmacol*. 2010



phenethyl (*E*)-3-**(3,4-dihydroxyphenyl)acrylate**

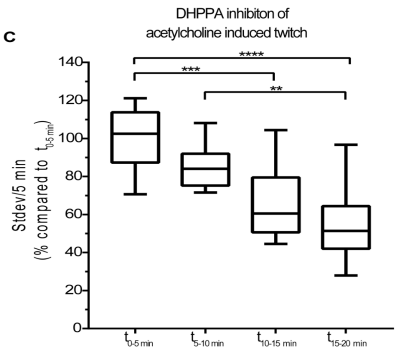


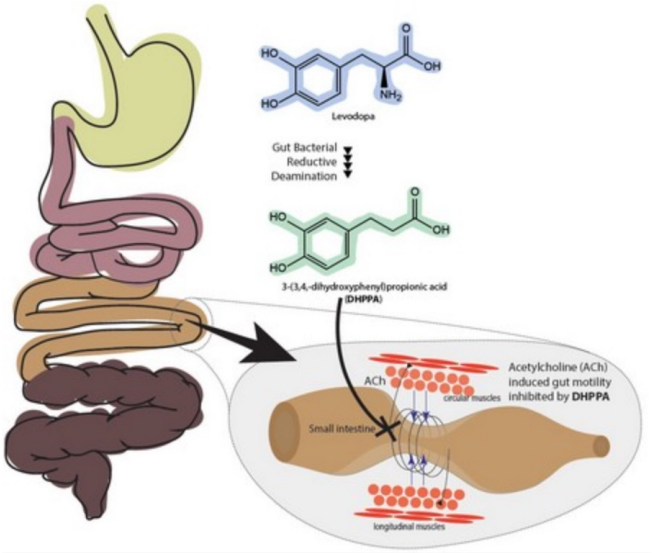
3-hydroxy-3-**(3-hydroxyphenyl)propanoic acid**

Negatively associated with gut transit time

Roagger et al. *Nat Microbiol*. 2016

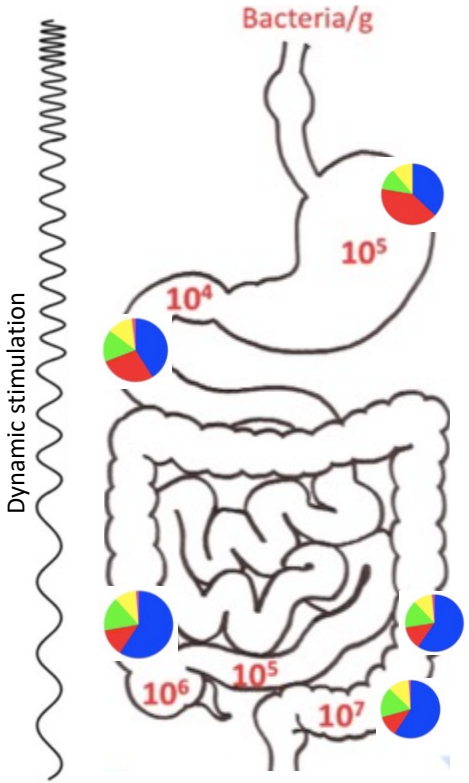
Unabsorbed Resides of Levodopa & Delayed Intestine Transit Time

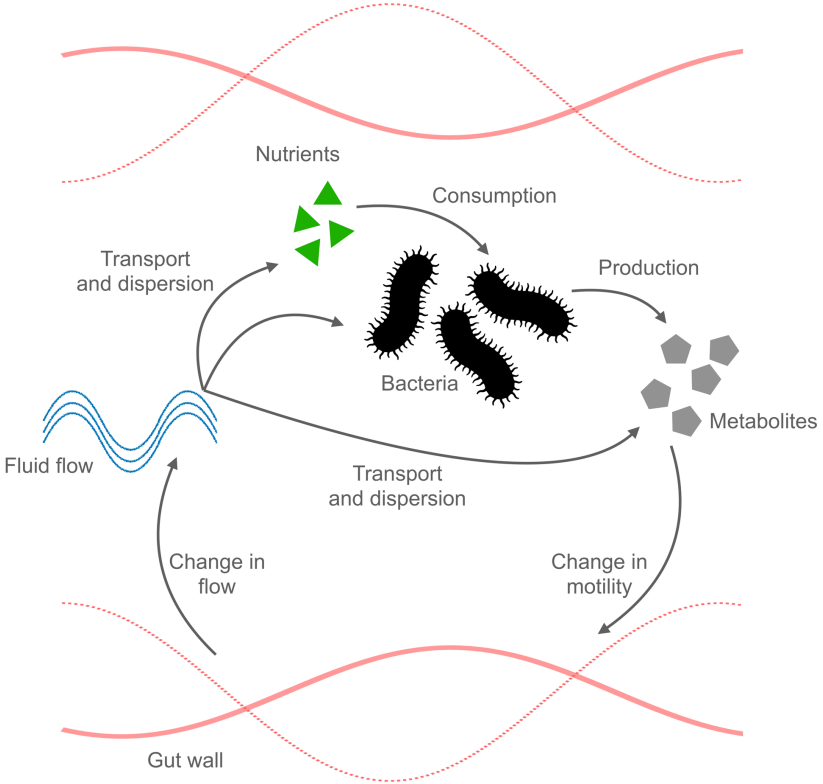




van Kessel S., et al., BMC Biol. (2020) 18:137.

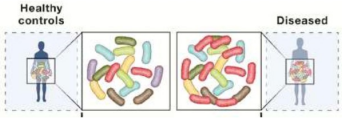
Gut microbiota-motility inter-regulation

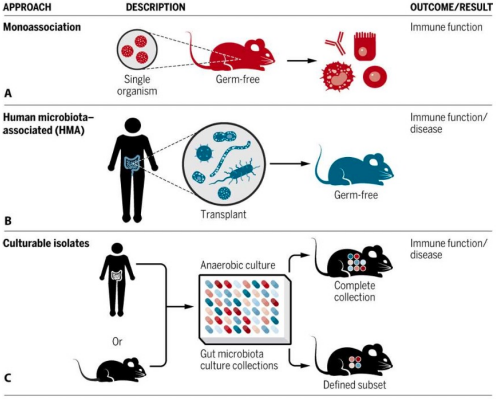




Waclawiková, B., et al.. Gut microbes 14 (1), 1997296, 2022

From Bench to Bedside





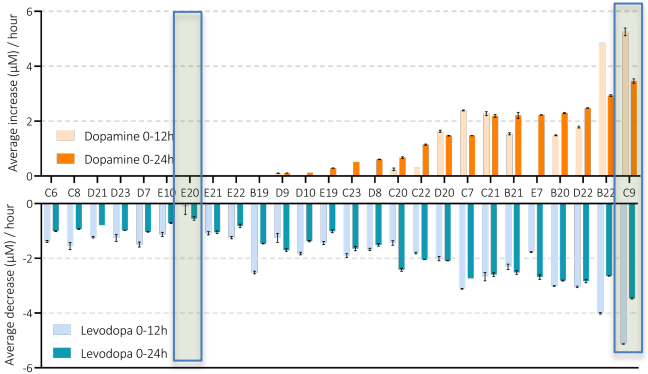
Observation in independent cohorts

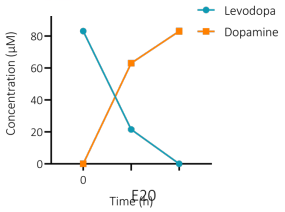
Explore mode of action

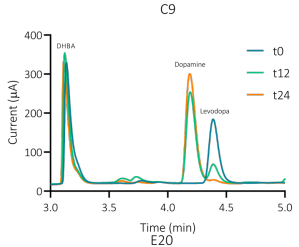
- Test TDC activity in longitudinal *de novo* cohort (>600 PD patients)
- Design of anti-microbials targeting TDC-harboring bacteria

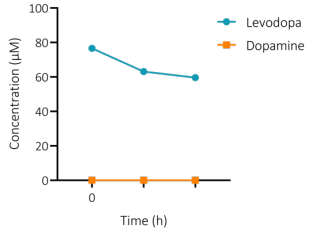
TDC Activity as a Stratification Tool to Enhance Medication Response in Parkinson's Disease Patients

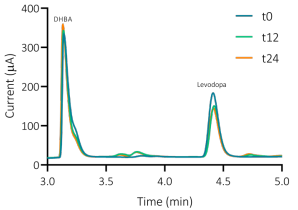
- Test TDC activity in longitudinal *de novo* cohort (>600 PD patients)
- Target TDC-harboring bacteria











Sieders, M. et al., unpublished

Summary

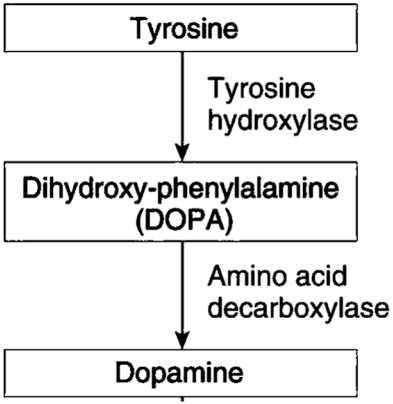
- The small intestinal microbiota, despite its low number of resident bacteria, high flow rate, and short transit time, has the potential to impact drug bioavailability.

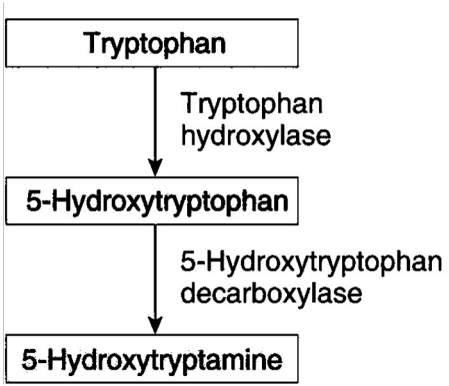
- The primary PD medications could potentially alter the composition of the microbiota and generate a state of SIBO by affecting small intestinal motility, the primary site of drug absorption.

- The unabsorbed residues of levodopa can be metabolized by colonic bacteria into different compounds that can influence intestinal motility.

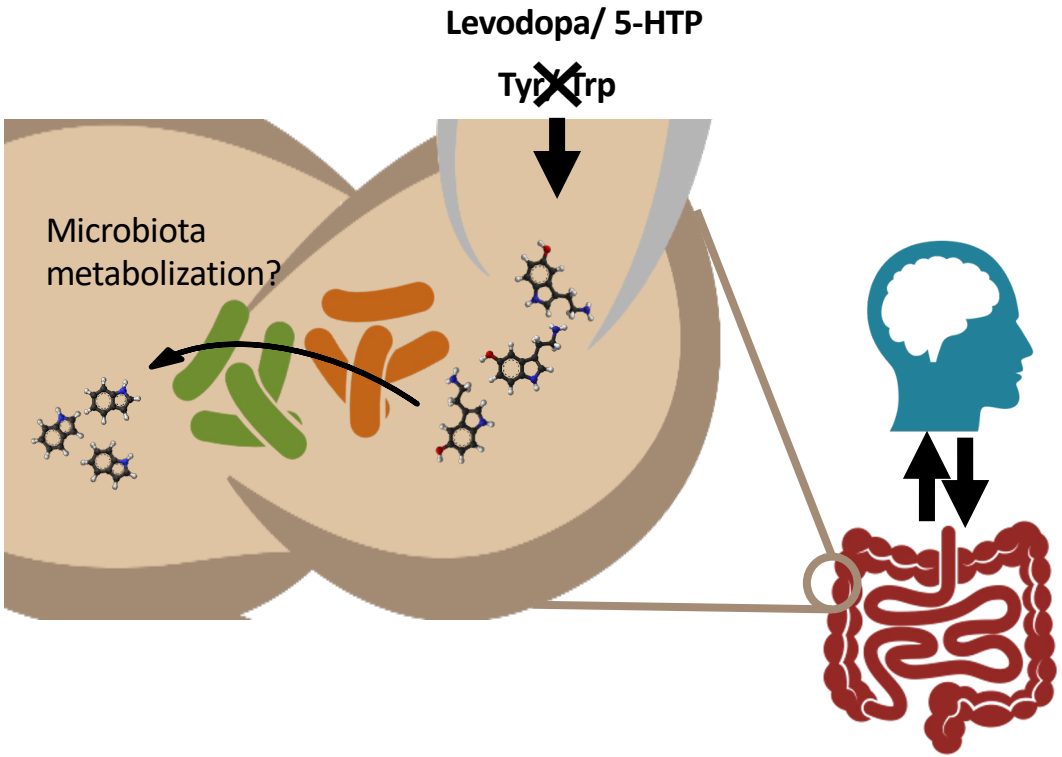
The site of absorption in the gut plays a crucial role in the gut bacteria-driven chemical transformation of drugs

Gut Bacteria and Neurotransmitters: Verifying Production Claims

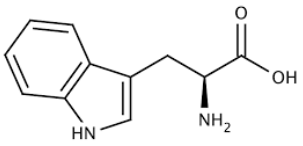




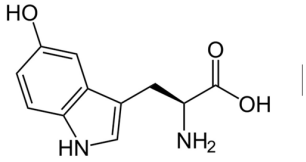
Host-Microbiome Metabolic Interactions



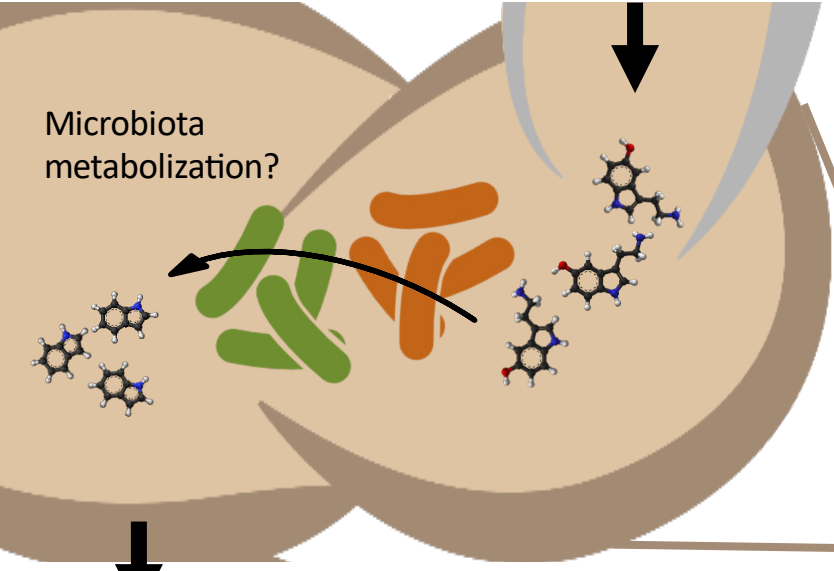
Host-Microbiome Metabolic Interactions



Tryptophan

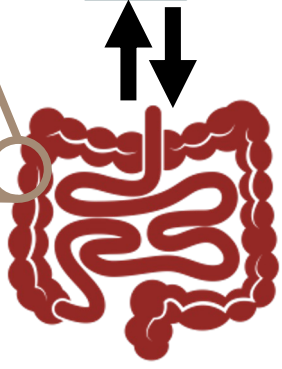


5-hydroxy-tryptophan



Indole

5-hydroxy-tryptophan

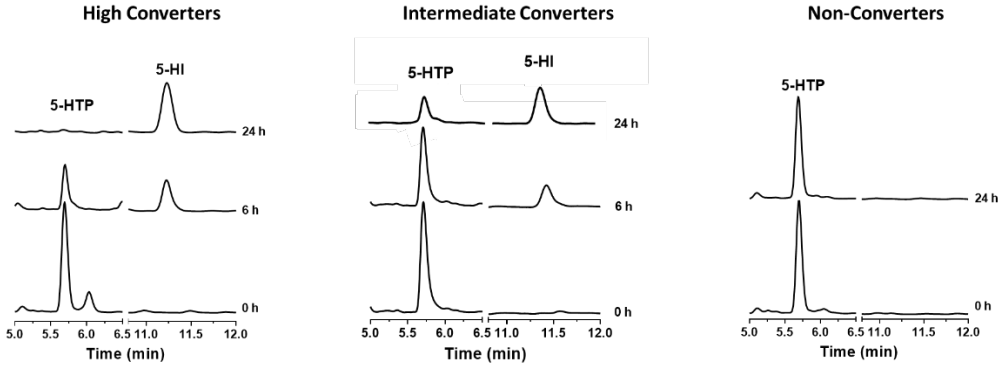


5-Hydroxytryptophan

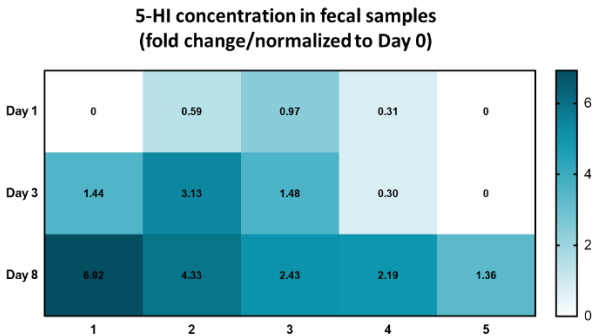
Food supplement

Co-medication with antidepressants

Gut microbiota converts 5-hydroxytryptophan to 5-hydroxyindole

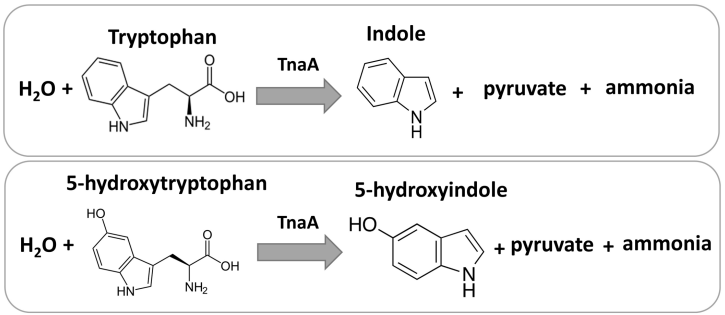


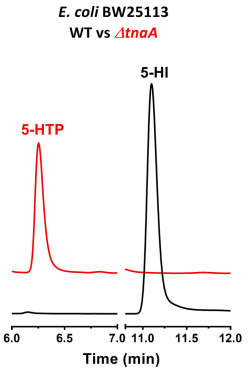
Human administration of 5-HTP

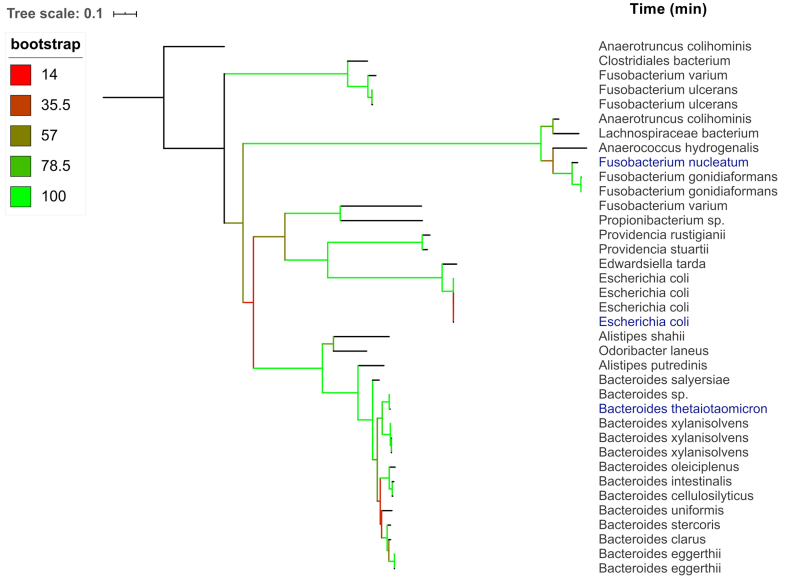


Waclawiková B., Bullock A., Schwalbe M., Aranzamendi C., Nelemans SA., van Dijk GJ., El Aidy S (2021) PLoS Biol 19(1): e3001070

Bacterial tryptophanase is responsible for the conversion of 5-HTP

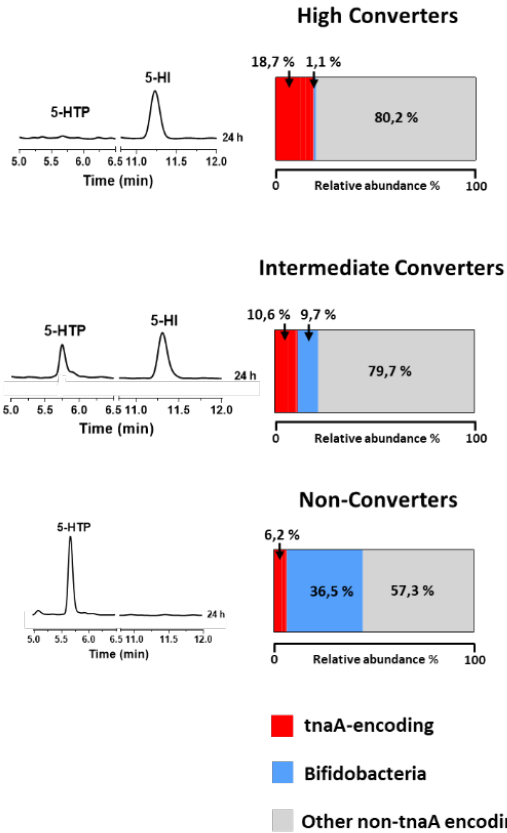


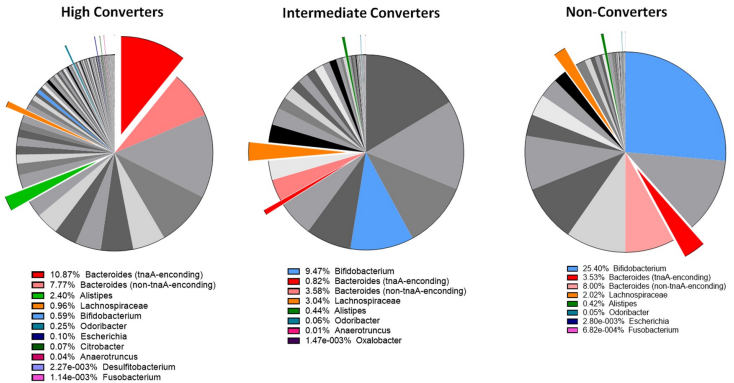




Waclawiková B., Bullock A., Schwalbe M., Aranzamendi C., Nelemans SA., van Dijk GJ., El Aidy S (2021) PLoS Biol 19(1): e3001070

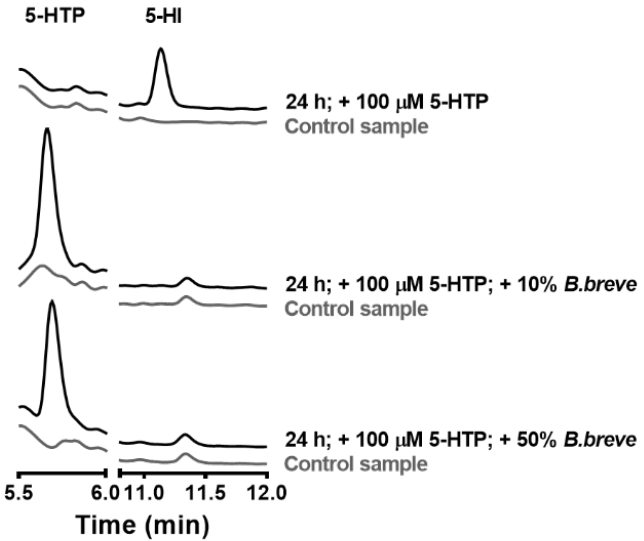
Bacterial production of 5-hydroxyindole is dependent on microbiota composition

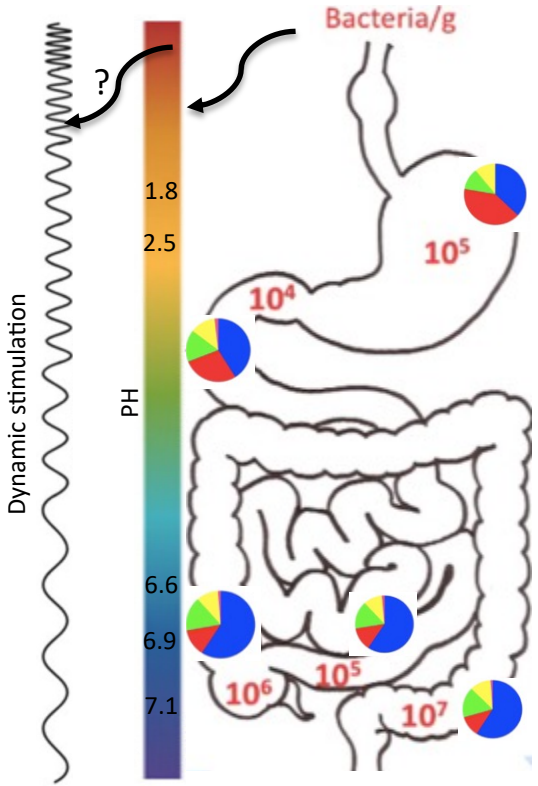




Waclawiková B., Bullock A., Schwalbe M., Aranzamendi C., Nelemans SA., van Dijk GJ., El Aidy S (2021) PLoS Biol 19(1): e3001070

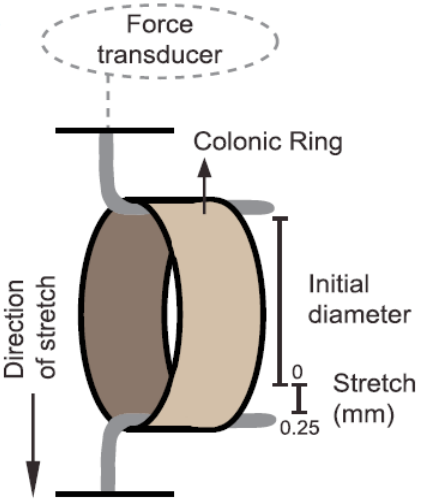
Reduction in pH results in a complete inhibition of the production of 5-hydroxyindole





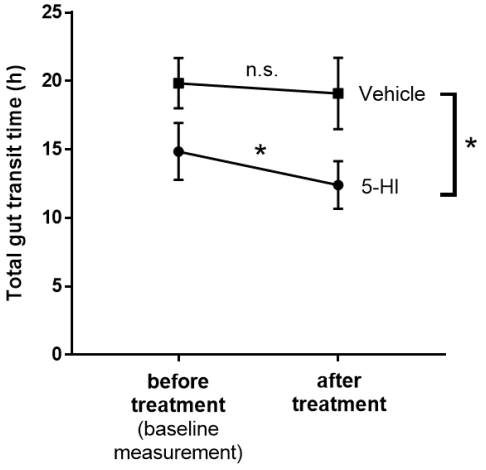
Waclawiková B., Bullock A., Schwalbe M., Aranzamendi C., Nelemans SA., van Dijk GJ., El Aidy S (2021) PLoS Biol 19(1): e3001070

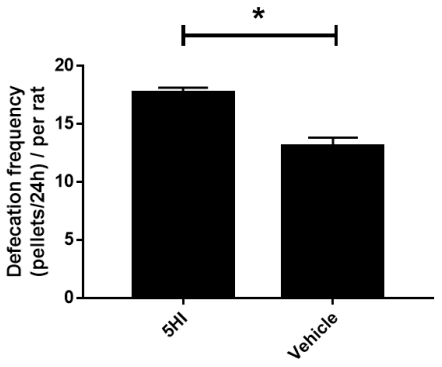
5-hydroxyindole is a potent stimulator of gut contractility *in vivo*



Ex vivo organ bath

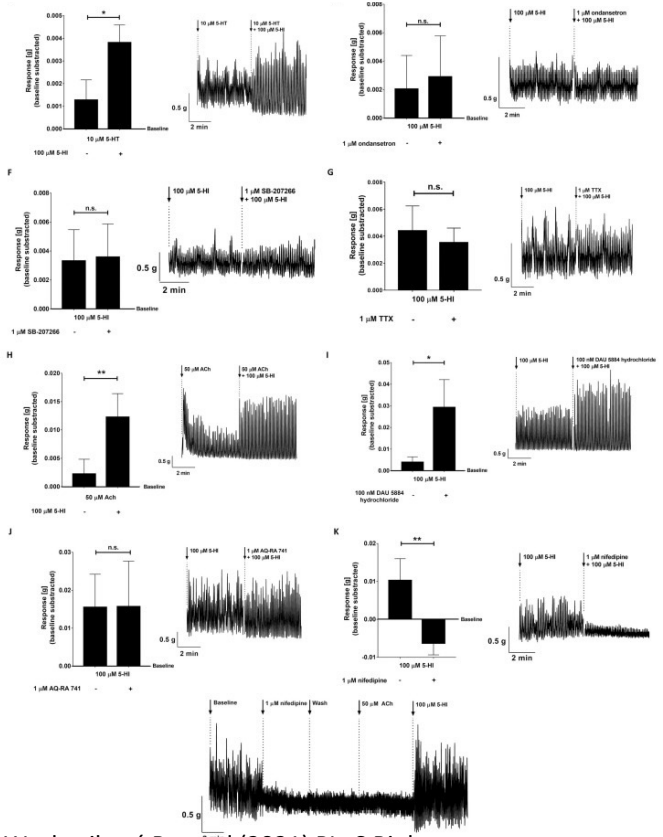
In vivo using Wild-type Groningen rats

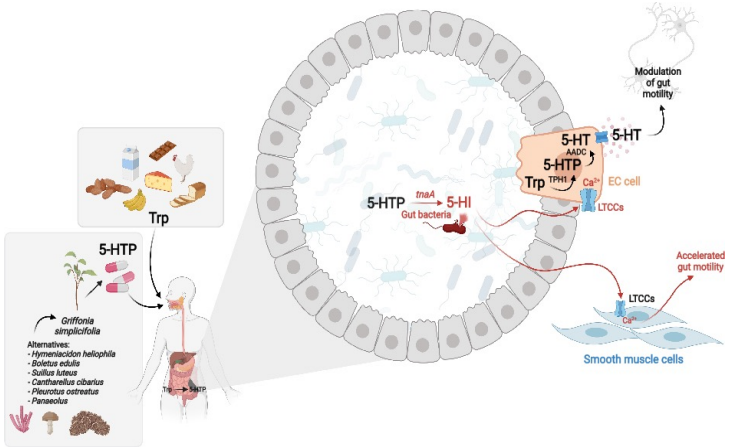




Waclawiková B., Bullock A., Schwalbe M., Aranzamendi C., Nelemans SA., van Dijk GJ., El Aidy S (2021) PLoS Biol 19(1): e3001070

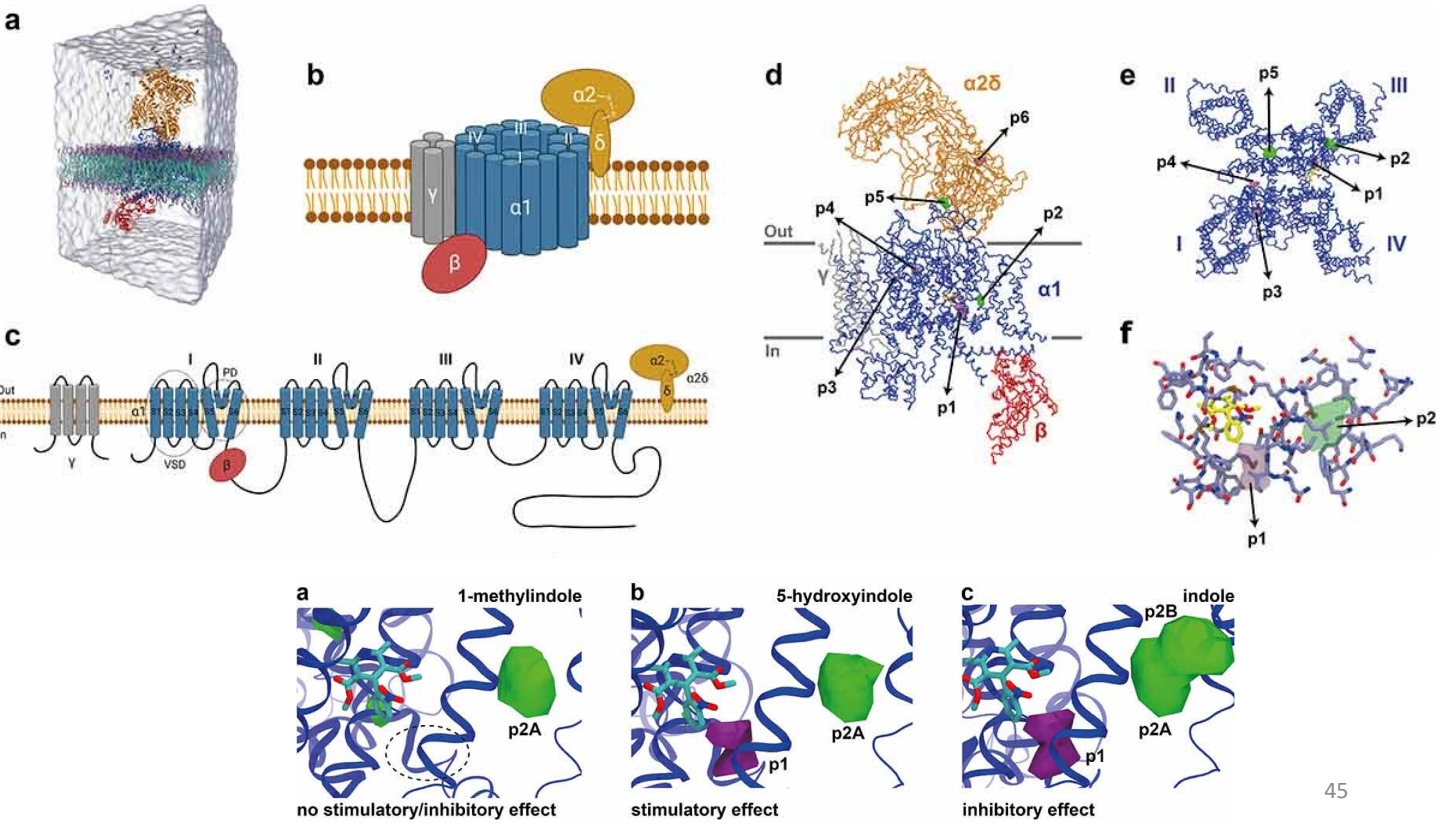
L-Type Voltage-Gated Calcium Channels Mediate the Gut Motility-Stimulating Effects of 5-Hydroxyindole





Waclawiková B., et al (2021) PLoS Biol
Waclawiková B., et al (2023) Gut microbes

5-Hydroxyindole Confirmed to Bind to α1 Subunit of L-Type Calcium Channels



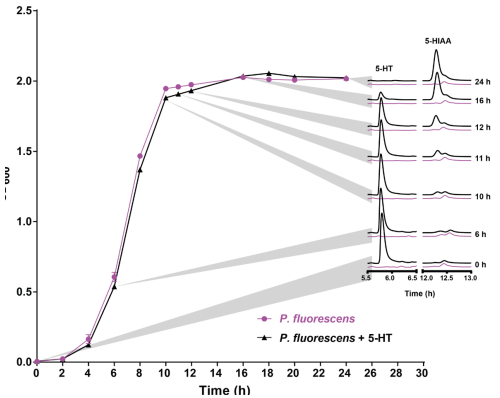
Summary

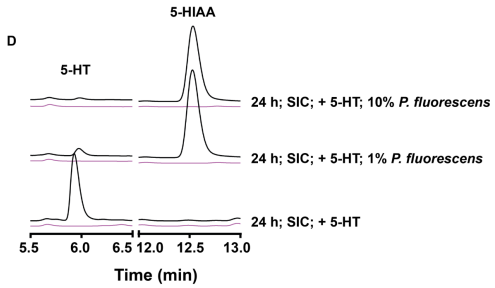
- Gut bacterial metabolic product; 5-hydroxyindole, plays an important role in inducing gut contractility, a comorbidity of various diseases as shown by *in vivo, ex vivo* experiments

- 5-hydroxyindole functions through the activation of L-type voltage dependent Ca^{2+} channels.

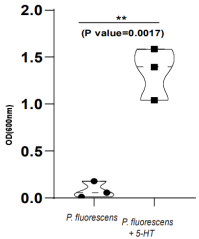
- 5-hydroxyindole may prove as a therapeutic targeted at modulating LVCCs function. So far, only 3 synthetic compounds are known to work as LVCCs agonists, none of which is approved clinically.

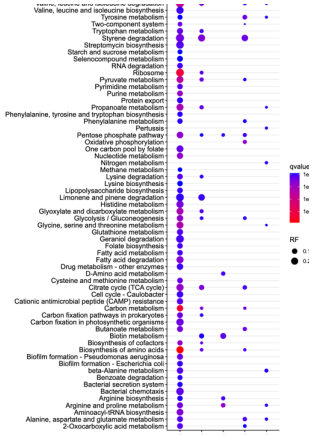
5-HT Conversion by Intestinal Bacteria

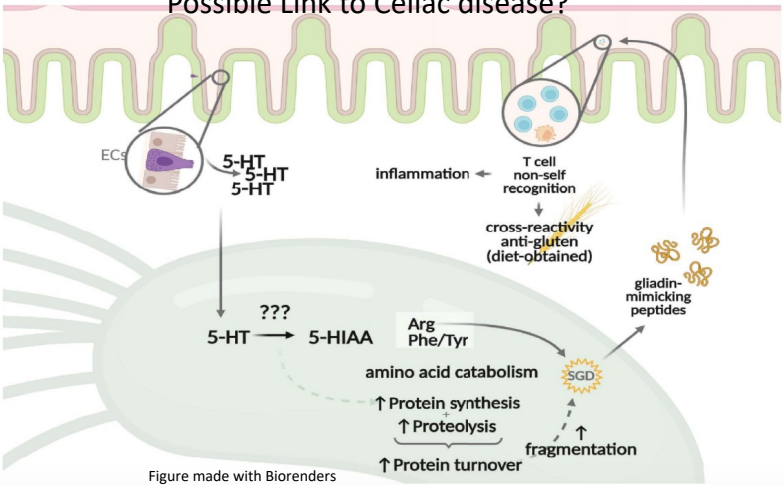




Serotonin Degradation by *P. fluorescens*; Possible Link to Celiac disease?



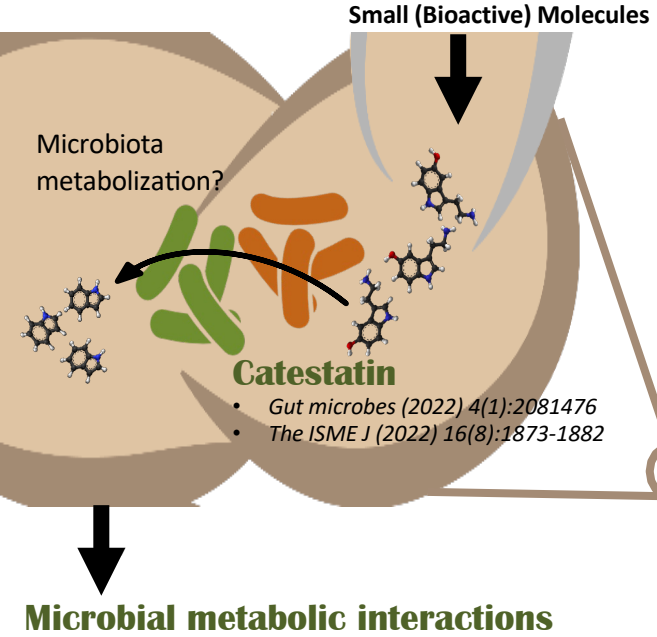




Anthi P., et al., unpublished

Beyond the Liver: Gut Microbiota and Drug Processing

Examples from the Lab

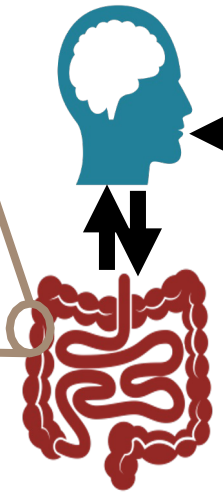


Catestatin

- *Gut microbes (2022) 4(1):2081476*
- *The ISME J (2022) 16(8):1873-1882*

Microbial metabolic interactions

- *Microbiome (2021) 9:16*
- *bioRxiv, 2023.03. 29.5346792*
- *bioRxiv, 2023.01. 29.525861*



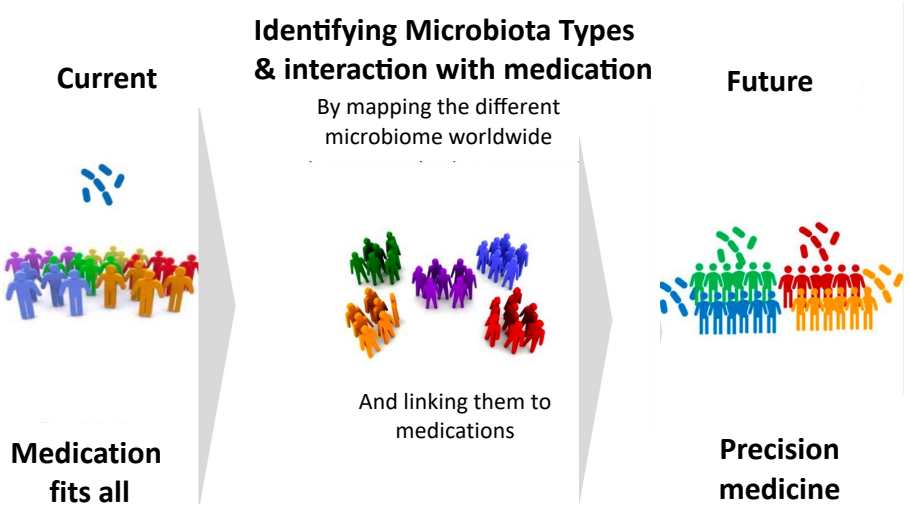
Levodopa

- *mSystems (2022) 22;7(1):e0119121*
- *NPJ Parkinson's disease (2021) 7 (1), 1-8*
- *BMC Biol. (2020) 18:137*
- *Front Neurol. (2019) 10:1087*
- *The Journal of Parkinson's Disease 9(s2):S359-S370*
- *Nature Communications, (2019) 10(1), [310]*

5-Hydroxyindole

- *Gut microbes (2023) 5(1):2154544*
- *Gut microbes (2022) 14 (1), 1997296*
- *WO Patent (2022) 2022010352*
- *PlosBiol (2021) 19(1) e3001070*
- *PharmaceuMcals, (2018) 11, 3, [63]*

Towards Precision medicine



Adapted after Veige et al., 2020

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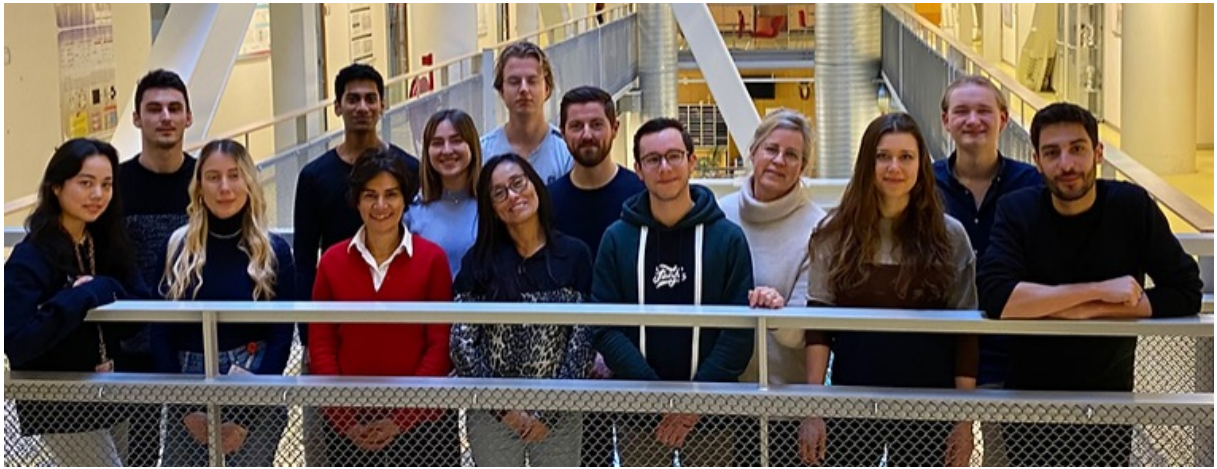
HMI Group



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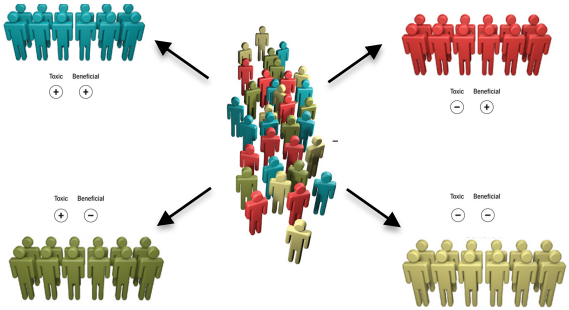
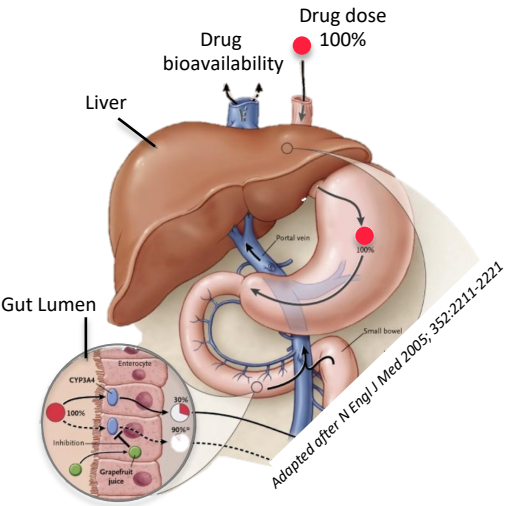
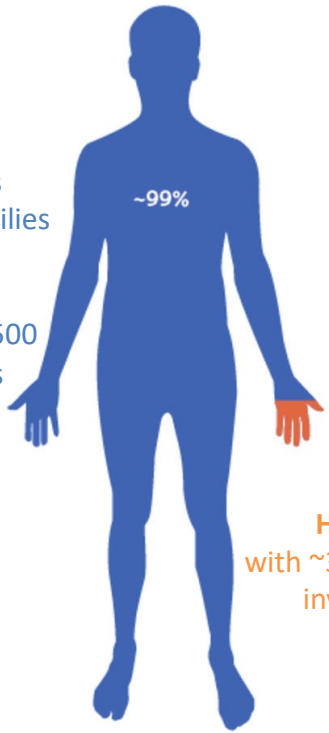
Microbial metabolic-host interactions





First-Pass Metabolism after oral administration of a drug

~2,000.000
Microbial genes
with (?) protein families involved in drug metabolism derived from 200-500 bacterial species



~23,000
Human genes
with ~30 protein families involved in drug metabolism

https://www.amnh.org/explore/science-topics/

➢ **Why would the microbiota harbor genes to metabolize drugs??**