Gut bacterial tyrosine decarboxylases restrict levels of levodopa in the treatment of Parkinson's disease

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Introduction

Parkinson's disease is the second most common neurodegenerative disorder, which is primarily treated by levodopa (L-DOPA)[1]. Previous research has shown that the microbiota-inhabiting human gut has a significant impact on the health of the host and indicate that microbiota have a crucial effect on many health and diseased states[2]. Additionally, studies show that gut microbiota can impact the efficacy of drug pharmacokinetics and drug bioavailability[3, 4]. Previous research supports investigation of mechanisms impacting L-DOPA treatments in Parkinson's disease because L-DOPA varies in efficacy of relieving symptoms among Parkinson's patients[5]. Still to be determined is whether inter-individual variations in gut microbiota composition play a causative role in the variation of L-DOPA treatment efficacy.

Tyrosine decarboxylase genes (*tdc*) are encoded in the genome of several bacterial species in the genera *Lactobacillus* and *Enterococcus*[6]. *Tdc* might have the ability to decarboxylate L-DOPA to produce dopamine[7], interfering with its bioavailability for therapeutic use.

Purpose

The purpose of the study is to analyze the effect of levodopa-metabolizing bacteria at it's primary site of absorption, the jejunum, and further use this information to understand the variability in L-DOPA dosage requirements for individual treatment of Parkinson's Disease.

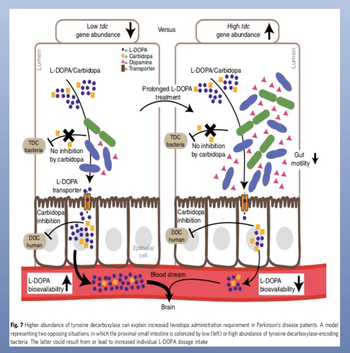

Fig. 7 Higher abundance of tyrosine decarboxylase can explain increased levodopa administration requirement in Parkinson's disease patients. A model representing two opposing situations, in which the proximal small intestine is colonized by low (left) or high abundance of tyrosine decarboxylase-encoding bacteria. The latter could result from or lead to increased individual L-DOPA dosage intake

Methods

To investigate whether natural variation of tyrosine decarboxylase relative abundance in the gut could interfere with L-DOPA uptake and decarboxylation, human fecal samples from Parkinson's patients on varying doses of L-DOPA/carbidopa, and jejunal content samples from rats on oral L-DOPA/carbidopa administration, were employed and tyrosine decarboxylase levels were detected. All data were ranked from low to high by tyrosine decarboxylase level and linear regression was performed with automatic outlier detection using the ROUT method in Graphpad Prism 7. Statistical tests performed were unpaired T-tests, 2-way-ANOVA followed by a Fisher's LSD test.

- **Human Fecal Sample**
  - n = 10
  - Parkinson's patients on variable doses of levodopa/carbidopa treatment
- **Rat Jejunal Content**
  - n = 25
  - Wild-type Groningen rats
  - treated with *E. faecalis* v583 cells followed by levodopa/carbidopa mixture
- **Analysis**
  - Quantitative PCR of *tdc* genes performed on DNA extracted from each human fecal sample & rat jejunal content samples

Results

It was determined that the bacteria of the upper small intestinal converts levodopa to dopamine. A higher relative abundance of bacterial Tyrosine decarboxylase genes (*tdc*) in stool samples of Parkinson's Disease patients positively correlated with higher daily levodopa/carbidopa dosage requirement and duration of disease.

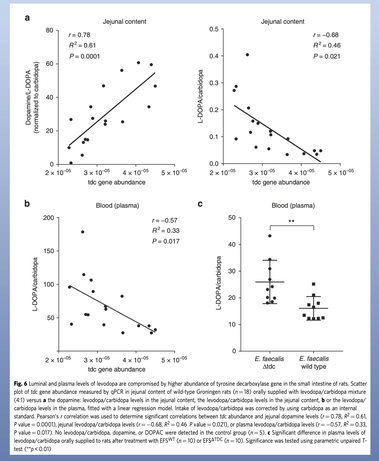

Fig. 6 Luminal and plasma levels of levodopa are compromised by higher abundance of tyrosine decarboxylase gene in the small intestine of rats. Scatter plot of tdc gene abundance measured by qPCR in jejunal content of wild-type Groningen rats ($n = 18$) orally supplied with levodopa/carbidopa mixture (4:1) versus **a** the dopamine: levodopa/carbidopa levels in the jejunal content, the levodopa/carbidopa levels in the jejunal content, **b** or the levodopa/carbidopa levels in the plasma, fitted with a linear regression model. Intake of levodopa/carbidopa was corrected by using carbidopa as an internal standard. Pearson's *r* correlation was used to determine significant correlations between tdc abundance and jejunal dopamine levels ($r = 0.78$, $R^2 = 0.61$, P value = 0.0001), jejunal levodopa/carbidopa levels ($r = -0.68$, $R^2 = 0.46$, P value = 0.021), or plasma levodopa/carbidopa levels ($r = -0.57$, $R^2 = 0.33$, P value = 0.017). No levodopa/carbidopa, dopamine, or DOPAC were detected in the control group ($n = 5$). **c** Significant difference in plasma levels of levodopa/carbidopa orally supplied to rats after treatment with EFS^{WT} ($n = 10$) or $EFS^{\Delta TDC}$ ($n = 10$). Significance was tested using parametric unpaired T-test (**$p < 0.01$)

Results

All p-values in the study were ≤ 0.05, indicating that the strength of the evidence is high. The r-coefficient for the *tdc* abundance and jejunal dopamine levels indicated the strongest positive correlation, while *tdc* abundance and jejunal levodopa/carbidopa levels or plasma levodopa/carbidopa levels both demonstrated fairly strong negative correlations:

- *tdc* abundance and jejunal dopamine levels
  - r = 0.78, P value 0.0001
- *tdc* abundance and jejunal levodopa/carbidopa levels
  - r = -0.68, P value 0.021
- *tdc* abundance and plasma levodopa/carbidopa levels
  - r = -0.57, P value 0.017

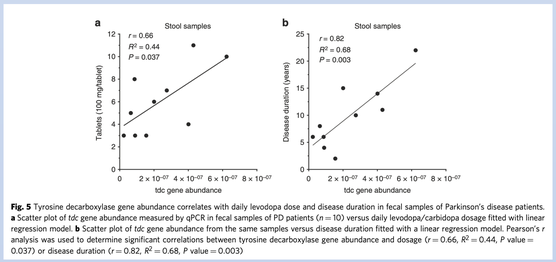

Fig. 5 Tyrosine decarboxylase gene abundance correlates with daily levodopa dose and disease duration in fecal samples of Parkinson's disease patients. **a** Scatter plot of *tdc* gene abundance measured by qPCR in fecal samples of PD patients ($n = 10$) versus daily levodopa/carbidopa dosage fitted with linear regression model. **b** Scatter plot of *tdc* gene abundance from the same samples versus disease duration fitted with a linear regression model. Pearson's *r* analysis was used to determine significant correlations between tyrosine decarboxylase gene abundance and dosage ($r = 0.66$, $R^2 = 0.44$, P value = 0.037) or disease duration ($r = 0.82$, $R^2 = 0.68$, P value = 0.003)

Conclusions

The authors conclude that levodopa conversion by bacterial *tdc* in the small intestine should be considered as a significant explanatory factor for the increased levodopa/carbidopa dosage regimen in a subset of Parkinson's patients. Therefore, bacteria or their encoded *tdc* gene may serve as a predictive biomarker to stratify Parkinson's patients for efficacy of levodopa treatment.

References

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