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 investigations 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.

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.

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.

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