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The gut microbiota: A novel therapeutic target in Parkinson's disease?

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The gastrointestinal microbiota (GM) have become an increasingly topical area in the quest to better understand the pathogenesis of Parkinson's disease (PD). Multiple studies have shown alterations in the GM of PD cohorts [1], suggesting a biomarker relevant to prodromal disease could be possible [2]. More recently, a novel approach to individualising PD treatment was identified when the bacteria that metabolise L-dopa to dopamine and *m*-tyramine (a phenomenon first identified in the 1970s) [3], were finally found.

Compelling research by Van Kessel et al. [4] and Maini Rekdal et al. [5] has proposed vital GM influences that moderate the metabolism of L-dopa. Studying the GM of PD patients, they showed that the enzyme tyrosine decarboxylase (TDC), predominately found within the GM, decarboxylates L-tyrosine to form tyramine and converts L-dopa to dopamine [4]. Screening human microbiome datasets, the genera *Lactobacillus* and particularly the species *Enterococcus faecalis*, were shown to have the TDC gene that catalysed the conversion of L-dopa to dopamine [4,5].

The Van Kessel et al. study further determined that these bacteria decarboxylated tyrosine and L-dopa in low pH environments, akin to the acidic environment of the jejunum where L-dopa is absorbed [4]. Intriguingly, the presence of tyrosine (a competitive substrate) or the DOPA decarboxylase inhibitors, carbidopa, benserazide and methyldopa (agents that block peripheral L-dopa metabolism), did not appear to inhibit TDC-dependent L-dopa conversion [4]. This suggests that in patients utilising combination L-dopa therapies, the efficacy of L-dopa conversion by the bacterial decarboxylases would not be affected [4]. Furthermore, this study also showed a positive correlation between higher levodopa/carbidopa dosage and disease duration being associated with the relative abundance of the bacterial TDC gene expression [4]. Finally, albeit in rats receiving L-dopa/carbidopa, they identified that a higher abundance of jejunal bacterial TDC genes corresponded to a lower plasma level of L-dopa. Thus, confirming that over-expression of bacterial TDC genes would result in a deleterious metabolism of L-dopa in the gut.

In the study by Maini Rekdal et al., a novel two-step interspecies pathway for GM L-dopa metabolism was revealed, whereby the conversion of L-dopa to dopamine by a pyridoxal phosphate-dependent TDC from *Enterococcus faecalis* was followed by transformation of dopamine to *m*-tyramine by a molybdenum-dependent dehydroxylase in the species *Eggerthella lenta* [5]. They further identified a polymorphism in the molybdenum-dependent dehydroxylase (p.Arg506Ser), that inactivated the enzyme and explained why < 50% of *Eggerthella lenta* strains dehydroxylated dopamine [5]. Such polymorphisms elegantly show the importance of understanding microbial metabolic function, rather than assuming comparable function based on taxonomic classification. The study further confirmed that carbidopa did not prevent bacterial L-dopa metabolism *in vivo*, as suggested by the Van Kessel study. They did however identify a small molecule inhibitor, α-fluoromethyltyrosine (AFMT), that prevented *in vitro* TDC-dependent L-dopa decarboxylation, as well as within *Enterococcus faecalis* cultures and GM samples from PD patients [5]. They showed that co-administration of AFMT with levodopa/carbidopa to mice colonised with *Enterococcus faecalis*, blocked L-dopa degradation, in turn observing increased serum L-dopa concentrations. These observations were consistent with earlier shown inhibition of GM L-dopa metabolism *in vivo*.

The studies by Van Kessel and Maini Rekdal showed that inactivating TDC gene activity in *Enterococcus faecalis* terminated L-dopa decarboxylation [4,5]. Such discoveries offer a unique potential to personalise L-dopa treatment in PD, and potentially other GM metabolic pathways, for a variety of drug therapies. However, the effects of chronic L-dopa exposure to the GM need to be better understood first, identifying if certain selection pressures determine the relative abundances of TDC gene encoding bacteria and what potential implications polymorphisms of TDC and other enzymes mean for L-dopa efficacy. Furthermore, measures aimed at validating these findings in humans are needed to evaluate the safety and efficacy of co-administration of AFMT-like compounds with levodopa/carbidopa, as a means of regulating TDC activity *in vivo*. Particularly in the hope of ameliorating the variability of L-dopa bioavailability and motor fluctuations.

Looking forward, the following strategies would be useful in validating the observations from these two studies in humans. Initially, human PD gut microbiome profiles could be evaluated to define relative abundances of *Enterococcus faecalis* and *Eggerthella lenta* strains. In addition, measurement of gut microbial TDC and L-dopa decarboxylase activities will be important to confirm consistency with findings from rat models [4] and delineate whether alterations to TDC gene expression reflect L-dopa levels in humans. This would provide an objective biomarker that could be further studied as an outcome measure, to predict the *in vivo* L-dopa bioavailability and efficacy and ultimately guide the management of motor fluctuations. Various study designs aimed at manipulating TDC gene expression should also be explored

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and could include lowering *Enterococcus faecalis* abundance with selective antimicrobials, repopulating the gut microbiome with alternate bacterial strains (such as with probiotics), or exploring the potential roles of selective faecal microbiota transplantation. Secondly, studies investigating the inhibition of L-dopa decarboxylation with TDC enzyme-blocking agents, such as AFMT [5], in addition to exploring the potential influences of inhibiting other catechol dehydroxylases, will provide valuable insights for predicting L-dopa bioavailability and therapeutic outcomes. Although AFMT has been shown to have increased efficacy in mice and gut microbiota samples from PD patients, initial human safety and tolerability studies are necessary prior to assessing its therapeutic efficacy. Lastly, further research examining the biological activity of the gut microbial metabolite *m*-tyramine in PD patients, in addition to the benefits of this metabolism for *Eggerthella lenta*, need to be determined. Collectively, the above strategies portray a novel understanding to the influences of the gut microbiota as predictive biomarkers for L-dopa metabolism, which will inform drug bioavailability, drug responsiveness and direct treatment outcomes.

In summary, these two pioneering studies highlight that specific GM and their enzymes can play an as yet underexplored and potentially vital role in the modulation of PD drug therapies. This opens a future to novel therapeutic options aimed at modifying the GM in PD. Whether it be through more extensive GM profile alterations, such as with antimicrobial and probiotic strategies, or more targeted approaches focusing on gut microbial TDC expression and other enzymatic pathways, the future certainly looks more promising as we begin to recognise the GM as a potential therapeutic target for PD.

Author contributions

Michal Lubomski: drafted and reviewed the manuscript.
Ryan L. Davis: drafted and reviewed the manuscript.
Carolyn M. Sue: drafted and reviewed the manuscript.

Author disclosures

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Conflicts of interest

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