A Possible Role Of Trans-Cinnamate In Parkinson's Disease: A Metabolomics Study Of An Egyptian Cohort

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Metabolomic Profiling Reveals Altered Phenylalanine Metabolism in Parkinson's Disease in An Egyptian Cohort

Research Questions

- *Is there any alteration in the metabolic profile of PD patients compared to that of the reference controls?*
- *Is it possible to identify the metabolic pathways that are altered?*

Key Studies

- PD is a complex progressive neurodegenerative disorder and the most common movement disorder globally. 5-10% of the PD cases are due to genetic causes, while the cause behind 90-95% of the PD cases is still unknown. The cardinal signs of PD involve motor symptoms such as tremors, bradykinesia/akinesia, postural instability, and rigidity. Additionally, PD is usually accompanied by non-motor symptoms such as autonomic nervous system dysfunction (orthostatic hypotension and constipation), depression, and/or sleep problems(1).

- Although, PD is pathologically characterized by the loss of the dopaminergic neurons in the midbrain, PD pathology affects other sites that includes non-dopaminergic neurons(2) such as adrenergic (noradrenaline-producing) neurons(3) and melatoninergic neurons(4).

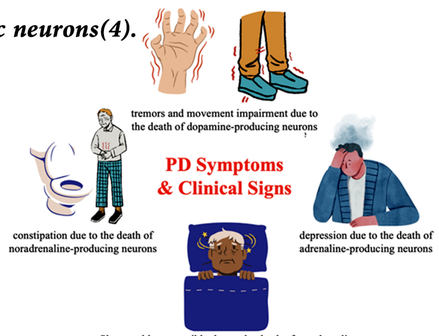

Figure 1 shows the most common signs and symptoms in PD and the possible cause for each of them.

- Phenylalanine is the precursor of the amino acid tyrosine and, subsequently, L-dopa and the neurotransmitters, dopamine and norepinephrine(5). Moreover the metabolism of phenylalanine is connected to the metabolism of tryptophan, the precursor of serotonin and melatonin(6). Although phenylalanine can be metabolized via 6 metabolic pathways, only 2 of which were studied(7). Thus, for the first time, we investigated the metabolism of phenylalanine via L-phenylalanine ammonia lyase (PAL) pathway.

- The metabolomics represents the collection of all metabolites in a biological organism(8).

Results

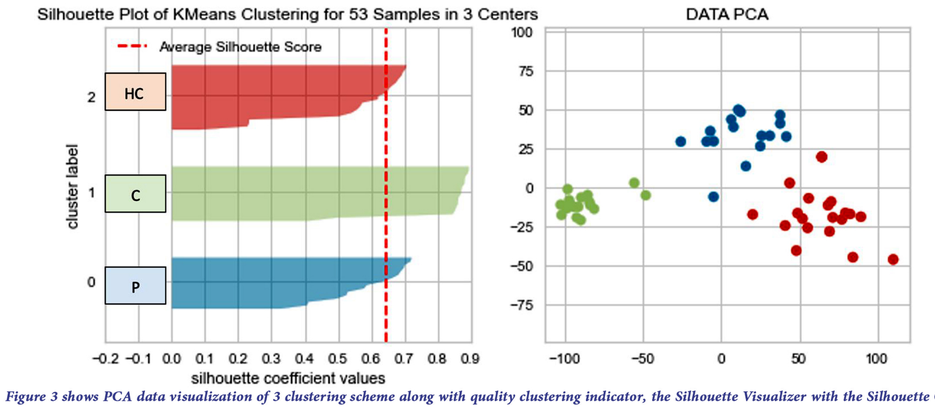

Figure 3 shows PCA data visualization of 3 clustering scheme along with quality clustering indicator, the Silhouette Visualizer with the Silhouette Coefficient. The green dots represent the reference controls (C), and the blue dots are the PD patients (P), while the red dots are the high-risk controls (HC). This figure shows how the C are significantly separated from P, and how P is significantly separated, to a lesser extent, from HC. Moreover, the figure exhibits that both P and HC are significantly separated from C.

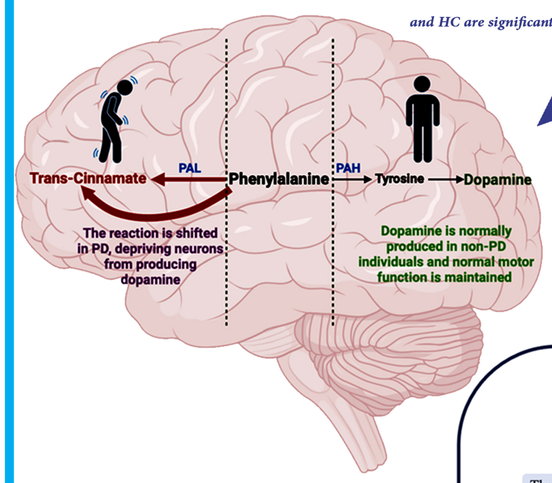

Figure 4 illustrates our novel finding, which hypothesizes a metabolic reaction shift of phenylalanine into producing trans-cinnamate instead of tyrosine and dopamine in PD patients in opposite to reference controls.PAH: Phenylalanine Hydroxylase. PAL: Phenylalanine Ammonia Lyase.

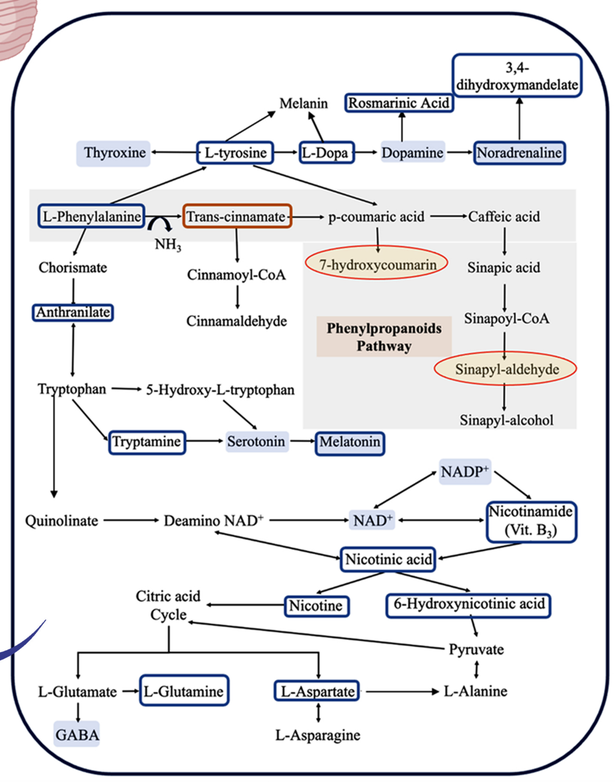

Figure 5 The metabolic pathways for the tackled metabolites. Compared to reference controls, the blue boxes show the metabolites that are significantly lower in patients, while the orange box shows the metabolite that is significantly higher in patients. On the other hand, the yellow shaded circles represent the metabolites that appear in patients only and not in controls, while the blue shaded metabolites are some molecules that have a role in developing the clinical symptoms of PD according to literature. This pathway was derived from KEGG database.

Methodology

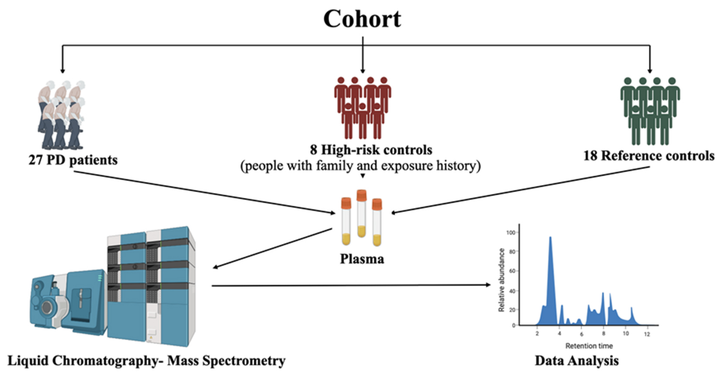

Figure 2 illustrates the study methodology .

Conclusion

In our study, we have introduced the switch in phenylalanine metabolism as potential contributor to PD pathogenesis. Based on our findings, we hypothesize that the switch between PAH to PAL- phenylalanine metabolic pathways, produces higher amounts of trans-cinnamate instead of the proper amount of tyrosine. As a result, there is a severe decrease in the production of dopamine and significant alterations in the metabolism of several interconnected metabolites such as norepinephrine, thyroxine, and melanin. Being connected to phenylalanine metabolism, tryptophan and citrate cycle metabolism have also been affected. These alterations were reflected on the levels of their metabolites such as serotonin, melatonin, nicotinamide (NAD precursor), and some non-essential amino acids such as L-alanine, L-glutamine (L-glutamate and GABA precursor), and L-aspartate. Based on the literature, most of these altered metabolites have been associated with several signs and symptoms of PD. Thus, we assume that this metabolic shift may be a possible initiator of the dopaminergic, adrenergic, and serotonergic neurodegeneration in PD as a complex metabolic disorder.

References

1- Peball, M., Krismer, F., Knaus, H.-G., Djamshidian, A., Werkmann, M., Carbone, F., Ellmerer, P., Heim, B., Marini, K., Valent, D., Goebel, G., Ulmer, H., Stockner, H., Wenning, G. K., Stolz, R., Krejcy, K., Poewe, W., Seppi, K., & Collaborators of the Parkinson's Disease Working Group Innsbruck. (2020). Non-Motor Symptoms in Parkinson's Disease are Reduced by Nabilone. Annals of Neurology, 88(4), 712–722. https://doi.org/10.1002/ana.25864

2- Simon, D. K., Tanner, C. M., & Brundin, P. (2020). Parkinson Disease Epidemiology, Pathology, Genetics and Pathophysiology. Clinics in Geriatric Medicine, 36(1), 1–12. https://doi.org/10.1016/j.cger.2019.08.002.

3- Espay, A. J., LeWitt, P. A., & Kaufmann, H. (2014). Norepinephrine deficiency in Parkinson's disease: The case for noradrenergic enhancement. Movement Disorders, 29(14), 1710–1719. https://doi.org/10.1002/mds.26048.

4-Breen, D. P., Nombela, C., Vuono, R., Jones, P. S., Fisher, K., Burn, D. J., Brooks, D. J., Reddy, A. B., Rowe, J. B., & Barker, R. A. (2016). Hypothalamic volume loss is associated with reduced melatonin output in Parkinson's disease. Movement Disorders: Official Journal of the Movement Disorder Society, 31(7), 1062–1066. https://doi.org/10.1002/mds.26592.

5- Kohlmeier, M. (2003). Phenylalanine. In M. Kohlmeier (Ed.), Nutrient Metabolism (pp. 314–321). Academic Press. https://doi.org/10.1016/B978-012417762-8.50051-X.

6- KEGG PATHWAY: Phenylalanine metabolism—Homo sapiens (human). (n.d.). Retrieved September 9, 2023, from https://www.genome.jp/pathway/hsa00360

7- Kaufman, S. (1999). A model of human phenylalanine metabolism in normal subjects and in phenylketonuric patients. Proceedings of the National Academy of Sciences, 96(6), 3160–3164. https://doi.org/10.1073/pnas.96.6.3160

8- Gomase, V. S., Changbhale, S. S., Patil, S. A., & Kale, K. V. (2008). Metabolomics. Current Drug Metabolism, 9(1), 89–98. https://doi.org/10.2174/138920008783331149

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