World Academy of Science, Engineering and Technology
International Journal of Bioengineering and Life Sciences
Vol:17, No:09, 2023

Tryptophan and Its Derivative Oxidation via Heme-Dioxygenase Enzyme

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Abstract : Tryptophan oxidation by Heme-dioxygenase enzyme is the initial rate-limiting step in the kynurenine pathway, which leads to the formation of NADH and dangerous metabolites, implicating several severe diseases such as Parkinson's Disease, Huntington's Disease, poliomyelitis and cataract. This oxidation, generally, allows tryptophan to convert to N-Formylkynurenine (NFK). Observing the catalytic mechanism of Heme dioxygenase in tryptophan oxidation has been a debatably scientific interest since no one has yet proven the mechanism obviously. In this research we have attempted to prove mechanistic steps of tryptophan oxidation via human indoleamine dioxygenase (h-IDO) utilising various substrates: L-tryptophan, L-tryptophan (indole-ring-2-^{13}C), L-fully-labelled^{13}C-tryptophan, L-N-methyl-tryptophan, L-tryptophanol and 2-amino-3-(benzo(b)thiophene-3-yl) propanoic acid. All enzyme assay experiments were measured using a UV-Vis spectrophotometer, LC-MS, 1H-NMR and HSQC. We also successfully synthesised enzyme products as our control in NMR measurements. The result exhibited that all substrates produced N-formyl kynurenine (NFK), and a side, the minor product of hydroxypyrrolloindoleamine carboxylic acid (HPIC) in cis and trans isomer, except 1-methyl tryptophan only generating cis HPIC. Interestingly, L- tryptophanol was oxidised to form HPIC derivative as a major product and 5-hydroxy tryptophan was converted to NFK derivative instead without any HPIC derivative. The bizarre result of oxidation underwent in 2-amino-3-(benzo(b)thiophene-3-yl) propanoic acid, which produced epoxide cyclic. Those phenomena have been explainable in our research based on the proposed mechanism of how tryptophan is oxidised by human indoleamine dioxygenase.

Keywords : tryptophan oxidation, heme-dioxygenases, human indoleamine dioxygenases, N-formylkynurenine, hydroxypyrroloindoleamine carboxylic acid
Conference Title : ICSB 2023 : International Conference on Structural Biology
Conference Location : Prague, Czechia
Conference Dates : September 04-05, 2023