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ABSTRACT

Characterization of the Intermediates of Heme Bound Peptides and Synthetic Analogues Associated with Amyloidogenic Diseases

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Peptides and proteins have been found to possess an inherent tendency to convert from their native functional states to misfolded amyloid aggregates. This phenomenon is associated with a range of increasingly common human disorders, including Alzheimer's (AD) and Parkinson diseases (PD), Type 2 Diabetes mellitus (T2Dm), and other systemic amyloidosis. A significant role of heme in the disease progression is confirmed and experimentally it has been found that heme can bind small peptides to form heme-peptide complexes, having detrimental effects. So, understanding the active site environment and consequent reactivity of these complexes can lead us to comprehend the cause and effect of these diseases to a fruitful therapeutic path in future. The main focus of the present thesis can be broadly categorised in (1) Investigating the role of heme in amyloidogenic diseases where a heme bound insulin complex has been found. Spectroscopically under different conditions like in presence of excess peptide and in varying pH, the change of active site of this complexes have been studied. The resultant heme-insulin complexes in their reduced state are found to produce very little PROS on getting oxidized by molecular O_2, although they have a higher peroxidase activity than that of free heme. (2) Trapping and characterisation of the plausible heme based reactive intermediates in the peroxidase pathway of heme-Aβ and heme-insulin complexes. The high-valent intermediates can interact with the essential biomolecules, proteins etc., hampering their normal biological functions. (3) Probing the role of second sphere in tuning the reaction pathway and the related intermediates which they generate in between. For this, different synthetic porphyrins are reacted with m-CPBA and they produce different final products via homolytic/heterolytic O-O bond cleavage of compound 0 (Fe-peroxo complex) and lastly (4) The probable *in-vitro* way of sequestering heme to get rid of heme-based cytotoxicity in physiological conditions. Using apomyoglobin, heme can be removed from heme bound peptides and this not only potentially diminishes heme-induced toxicity in the pancreatic β-cells but also produces Mb which has well-documented functions throughout the respiratory system and can thereby likely reduce the risks associated with T2Dm. These works significantly contribute towards the ongoing 'Heme hypotheses' in the amyloidogenic diseases pathology.

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