Abstract

The present thesis entitled “Understanding role of Cu and Zn metal ions in the aggregation and toxicity of Aβ peptide” deals with the aggregation and toxicity of amyloid beta (Aβ) peptide involved in Alzheimer’s disease (AD). Aβ peptide is found to be aggregated in the extracellular region in brains of AD patients and the amyloid plaques are found to be hypermetalated with copper and zinc ions. The redox active metal ions are responsible for generating oxidative stress in the brain which leads to neurotoxicity. These metal ions are also known to bind the Aβ peptide and cause aggregation of the peptide. The work described in this thesis is divided into four chapters:

Chapter 1 reviews the literature on Alzheimer’s disease. It provides a background on the pathophysiology and treatments of AD. It also provides an account of metal ions, viz. copper and zinc, in the aggregation of Aβ peptide. Also, the involvement of oxidative stress in AD and the effects of oxidation of biomolecules especially proteins is discussed.

Chapter 2 describes the oxidation of Aβ peptide using pulse radiolysis. The reaction of hydroxyl radicals with Aβ1-16 peptide produced oxidized, dimeric and trimeric species of Aβ1-16 peptide. The major site of oxidation in Aβ peptide was found to be at His6, while the site for dimerization was at Tyr10. The oxidized Aβ peptide efficiently binds copper similar to that as the unoxidized Aβ peptide; and efficiently produce free radicals in presence of copper and ascorbate resulting into cell death.

Chapter 3 deals with the oxidation of Aβ-metal complexes using gamma radiolysis. Aβ1-16 peptide is oxidized to a greater extent in the presence of Cu(II) while Zn(II) does not affect the oxidation of Aβ1-16 peptide. The oxidation of residues Asp1, His6, and His13 was enhanced due to their involvement in copper binding. The oxidation of His residues of Aβ1-16 peptide, which are chiefly responsible for copper binding, resulted in altered redox properties and subsequently in higher cytotoxicity in SH-SY5Y cells.

Chapter 4 deals with the synthesis and characterization of thiosemicarbazone derivatives as potential therapeutics for treatment of AD. These compounds were found effective in inhibiting Aβ peptide aggregation and toxicity in SH-SY5Y cells. Additionally, these compounds were effective in rescuing the rough eye phenotype in Aβ(1-42) expressing Drosophila melanogaster fly models. The compounds also regulate autophagy in SH-SY5Y cells. Hence, thiosemicarbazone derivatives are prospective candidates in the treatment for AD.