Theoretical and Computational Approaches to the Chemistry of Alzheimer's Disease

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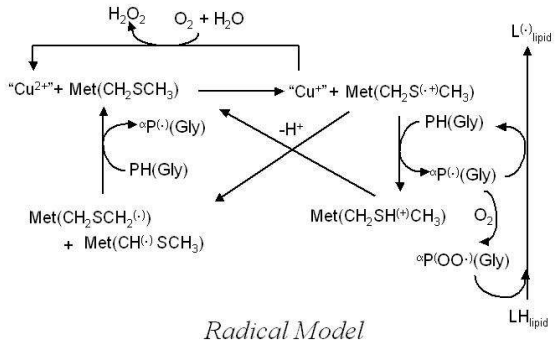
The central focus of research in our laboratory for a decade or more is the *Radical Model* of Alzheimer's Disease (AD). It is an extension of the *Amyloid Hypothesis* that states that the root cause of AD is the accumulation of the beta amyloid peptide (Aβ), and provides a comprehensive hypothesis of the chemistry that underlies AD. The premise is that the seminal event leading to the death of neuronal cells is damage to neuronal cell membranes caused by free radicals which initiate lipid peroxidation. In the *Radical Model*, these radicals are long-lived, hydrophobic glycyl radicals or their peroxy derivatives which are carried into the membrane by oligomers of the Aβ in β-sheet form. The glycyl radicals are secondary products of methionine oxidation by Aβ-complexed, redox active Cu(II). The structures, stabilities and reactivities of most of the radicals involved in the chain of events that starts with Aβ-bound Cu(II) and terminates in lipid peroxidation are examined in detail by high level computational methods. Special emphasis is placed on the initial step, the oxidation of methionine by the Cu(II)/Aβ complex and the structural and environmental requirements for raising the reduction potential of the Cu(II) and lowering that of the Met sulfide radical cation. Molecular dynamics simulations over timescales approaching a microsecond of free aqueous Aβ and its Cu(II) complexes are examined with a view to finding targets for the design of compounds that prevent the aggregation of Aβ into the toxic oligomeric form.



Radical Model