INVESTIGATING THE ACTIVATION OF INSULIN DEGRADING ENZYME (IDE) AND SELECTIVITY OF NEPRILYSIN (NEP)

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Activation of insulin degrading enzyme (IDE) by small molecules and modification in substrate selectivity of neprilysin (NEP) have been suggested as promising therapeutical approaches for the prevention of diabetes and Alzheimer`s disease. Recent experimental studies have shown that the polyphosphate anions activate IDE towards the hydrolysis of small fluorogenic peptide substrates (ca. 100-200 fold). We have combined molecular docking and molecular dynamics (MD) simulations to explore the potential binding sites for the activator of IDE, adenosine triphosphate (ATP), inside the catalytic chamber of the enzyme. Additionally, we have employed MD simulations to study the effect of experimentally proposed single and multiple mutations (Ser546Glu, Ser546Lys, Phe563Leu, Phe563Val, Ile558Phe, V580Ile, Val580Met) on the structure of the NEP, and also on the substrate (Aβ40, angI, and substance P) selectivity of the enzyme. These studies will help to obtain a deeper understanding on the activation of IDE and on the residues that play vital role in the mechanism of substrate selectivity of NEP.