The Crystal Structure of NEP and its Complexes with Inhibitors

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Neprysilin (NEP; EC 3.4.24.11) is a mammalian, zinc-dependant type II membrane protein consisting of a short N terminal cytoplasmic domain of 27 amino acids, a transmembrane region of 22 hydrophobic residues, and a large extracellular domain of some 700 residues. NEP has many functions in humans and is principally involved in turning off regulatory peptide signals in the brain as well as in the metabolism of a number of smaller regulatory peptides of the cardiovascular, inflammatory, and immune system. Its substrates include the enkephalins, substance P, atrial natriuretic factor, bradykinin, and endothelins. NEP down-regulated in a number of cancers, especially of the prostate. Lately it has been shown that NEP is involved in metabolism and removal of the neurotic amyloid β-peptide, the deposition of which in the brain is part of the initiation of Alzheimer's disease.

We describe the crystal structure of the soluble extracellular domain of rabbit NEP (residues 55-700) at 2.2 Å resolution. There are two molecules in the asymmetric unit and the structure reveals an extra metal molecule bound to the active site Zn, but not coordinated by NEP as well as several glycosylated residues. We have solved and refined the crystal structures of rabbit NEP complexed with competitive inhibitors, thiorphan and phosphoramidon at 3 Å and 2.8 Å resolution, respectively.

Keywords: macromolecular synchrotron x-ray crystallography, metalloprotein structures, enzyme inhibitors