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Inhibition of protein tyrosine phosphatase 1B *in vitro* and *in vivo*

A large number of studies of protein tyrosine phosphatases (PTPases) have been directed towards drug design for therapeutic intervention because of their critical roles in homeostasis and disorders of metabolism. In contrast to protein tyrosine kinases, virtually all inhibitors tested against PTPases exhibit only competitive behavior because of their consensus, active site sequence H/V-C-X5-R-S/T, a condition leading to low specificity. Having identified protein tyrosine phosphatase-1B (PTP1B) as the target enzyme of the vanadyl (VO2+) chelate bis(acetylacetonato)oxidovanadium(IV) [VO(acac)2] in cultured 3T3-L1 adipocytes [Ou et al. (2005) J. Biol. Inorg. Chem. 10, 874-886], we have investigated the basis of inhibition by the VO2+-chelate through steady-state kinetic investigations of the recombinant human enzyme (residues 1– 321). Our results differ from investigations by others because we compared the influence of the chelate in the presence of the synthetic substrate p-nitrophenylphosphate (pNPP) and the phosphotyrosine-containing undecapeptide DADEpYLIPQQG mimicking residues 988 – 998 of the epidermal growth factor receptor, a physiologically relevant substrate. We also compared the inhibitory behavior of VO(acac)2 to that of two other VO2+-chelates similarly known for their capacity to enhance cellular uptake of glucose as insulin mimetics. The results indicate that VO(acac)2 acts as a classical uncompetitive inhibitor in the presence of DADEpYLIPQQG but exhibits only apparent competitive inhibition with pNPP as substrate. Because uncompetitive inhibitors are more potent pharmacologically than competitive inhibitors, structural characterization of the site of uncompetitive binding of VO(acac)2 toPTP1B may provide a new approach to design of inhibitors of high specificity for therapeutic purposes.

Speaker Biography

Over the past 40 years at the University of Chicago, research in the Makinen lab has been directed towards the structural basis of enzyme action. Earlier research was focused on metalloenzymes and the application of magnetic resonance methods to characterize active site structure and stereochemical relationships of substrate atoms to catalytic residues in the active site in true reaction intermediates. More recent studies have been carried out to identify the target enzymes of metal-chelates that enhance the cellular uptake of glucose. Because some metal-chelates are associated with the capacity to enhance preferential uptake of glucose into xenograft tumors in small laboratory animal models, present research has been directed towards testing their potential as pharmacologic reagents to increase sensitivity of detection of malignant lesions by PET imaging.

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