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

A large number of studies on protein tyrosine phosphatases (PTPases) have been directed towards drug design fo 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-X 5-R-S/T, a condition leading to low speci city. Having identi ed protein tyrosine phosphatase-1B (PTP1B) as the target enzyme of the vanadyl (VO^{2+}) chelate bis(acetylacetonato)oxidovanadium(IV) [$VO(acac)_2$] in cultured 3T3-L1 adipocytes, we have investigated the basis of inhibition by the VO^{2+}-chelate through steady-state, kinetic investigations of the recombinant human enzyme (residues 1-321). Our results di er from investigations by others because we compared the in uence 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 VO^{2+}-chelates similarly known for their capacity to enhance cellular uptake of glucose as insulin mimetics. e 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 $VO(acac)_2$ to PTP1B may provide a new approach to design of inhibitors of high speci city for therapeutic purposes.

Biography

Marvin W. Makinen is Professor in the Department of Biochemistry and Molecular Biology in The University of Chicago, USA and has served as chairman of the department from 1988 to 1993. He is also a founding member of the Human Rights Board at the university. He did his D.Phil., in the year 1976 in Molecular Biophysics at Oxford Univer- VLW\ 8 . 2YHU WKH SDVW \HDUV DW 7KH 8QLYHUVLW\ RI &KLFDJR UHVHDUFK LQ WKH 0DNLQHQ ODE KDV E WKH DSSOLFDWLRQ RI PDJQHWLF UHVRQDQFH PHWKRGV WR FKDUDFWHUL]H DFWLYH VLWH VWUXFWXUH DQG LQWHUPHGLDWHV 0RUH UHFHQW VWXGLHV KDYH EHHQ FDUULHG RXW WR LGHQWLI\ WKH WDUJHW HQ]\PHV 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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