Ang Sherpa, Biochemistry

University: College of Saint Elizabeth
Year in School: Junior
Hometown: Kathmandu, Nepal and Morristown, New Jersey
Faculty Mentor: Dr. Kent S. Gates, Chemistry
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Inactivation of PTP1B by endogenous and dietary aldehydes

Ang Doma Sherpa, Derrick R. Seiner, and Kent S. Gates

Protein tyrosine phosphatase-1B (PTP1B) plays a significant role in the tyrosine phosphorylation-dependent signal transduction by dephosphorylating the tyrosine residue in the insulin signaling pathway. PTP1B has a catalytic cysteine residue (Cys 215) at the active site. Knockout studies have shown that there is an enhancement of insulin sensitivity and obesity resistance in mice without the gene for PTP1B, making the enzyme a target for treatment of Type II diabetes. Efforts are ongoing in the search for the drug inhibitors of PTP-1B. It is also crucial to identify endogenous and/or dietary inhibitors of the enzyme. For instance, aldehydes are consumed in diet and generated by lipid metabolism. They are also known as inhibitors of cysteine dependent enzymes. Accordingly, we have studied acrolein, an unsaturated aldehyde, and investigated whether it can act as an endogenous /dietary inhibitor of PTP1B. Indeed, we find that acrolein inactivates PTP1B and is higher in potency than hydrogen peroxide, the known endogenous regulator of PTP1B activity. The inactivation of PTP1B by acrolein is irreversible. The inhibition is active site directed which is confirmed by the use of a competitive inhibitor phosphate. We find that simple aldehydes lacking conjugated double bonds are not inactivators of PTP1B. In conclusion, we can say that acrolein is a powerful inactivator of PTP1B and the inactivation of PTP1B proceeds through addition at the double bond not at the carbonyl group of acrolein.