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Preferential Peroxidase Activity of Prostaglandin Endoperoxide H Synthase for Lipid Peroxides

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Prostaglandin endoperoxide H synthase (PGHS) catalyzes the committed step in prostaglandins and thromboxane A_2 -- oxygenation of arachidonic acid to the hydroperoxy endoperoxide PGG_2, followed by reduction PGG_2 to the alcohol PGH_2. The two reactions by PGHS -- cyclooxygenase and peroxidase -- occur at distinct but structurally and functionally interconnected sites. The peroxidase reaction occurs at a heme-containing active site located near the protein surface. The cyclooxygenase reaction occurs in a hydrophobic channel in the core of the enzyme. Initially a peroxide reacts with the heme group, yielding Compound I and an alcohol derived from the oxidizing peroxide. Compound I next undergoes an intramolecular reduction by a single electron traveling from Tyr385 along the peptide chain to the proximal heme ligand, His388, and finally to the heme group. Following the binding of arachidonic acid, Tyr385 tyrosyl radical initiates the cyclooxygenase reaction by abstracting the 13-pro(S) hydrogen atom to give an arachidonyl radical, which sequentially reacts with two molecules of oxygen to yield PGG_2. In order to characterize PGHS peroxidase active site, we examined various lipid peroxides with purified recombinant ovine PGHS proteins and determined the rate constants. The results have shown that twenty-carbon unsaturated fatty acid hydroperoxides have similar efficiency in peroxidation by PGHS, irrespective of either the location of hydroperoxy group or the number of double bonds. It was also confirmed by the subsequent study with PGHS peroxidase active site mutants.