

Putative model for glycosylated prostaglandin endoperoxide synthases

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Prostaglandin endoperoxide synthases (PGHSs) are homodimeric integral membrane enzymes, N-glycosylated, located in the endoplasmic reticulum lumen, which catalyze the first step in the prostanooids synthesis. PGHS-1 is constitutively expressed in several cell types, while PGHS-2 is usually expressed by induction. Both isoforms are glycosylated at residues Asn68, Asn144 and Asn410, in a process necessary for adequate cyclooxygenase and peroxidase activities of the enzymes. In PGHS-2 there is also a fourth residue that can be glycosylated, which is related to its degradation. Considering the available experimental information on PGHSs, the current work intends to analyze its glycosylation and so obtain a description of the complete three-dimensional structures. Based on such analysis, most of the crystallographic structures from the two isoforms of PGHS were observed to present poorly resolved glycans, with N-linked oligosaccharides that do not reflect the available biochemical data related to its post-translational modification. The well resolved structures, in agreement with other experimental data, supported the building of a putative model for the glycosylated PGHSs. Such models were further employed in a conformational analysis and comparison in both crystal and solution environments, supporting the identification of potential crystal packing forces and solution like conformations. Considering the participation of cyclooxygenases in several pathologies, such as inflammation and Alzheimer disease, the obtaining of a model for the complete PGHSs may be expected to contribute in the understanding of such diseases and, consequently, to contribute in the search of new therapeutic strategies. Supported by CNPq Universal (472174/2007-0) and CAPES.