Structure of Aldehyde Reductase Complex: Implications for Inhibitor Specificity

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Aldehyde and aldose reductases are members of the aldo-keto reductase superfamily of enzymes that catalyze the NADPH-dependent reduction of a number of different aldehydes to their corresponding alcohols. Both enzymes share significant sequence homology and form a classic α/β TIM-barrel structure with the least conserved residues lining the active site located at the C-terminal loop. Aldose reductase activity has been implicated in glucose over utilization and the aetiology of diabetic complications. Given the abilities of both enzymes to bind common inhibitors, the X-ray structure of porcine aldehyde reductase holoenzyme in complex with NADPH and the potent aldose reductase inhibitor Fidarestat (SNK-860) was determined at an atomic resolution of 1.85Å to elucidate the mechanism of inhibition. The hydrogen bonds between the active site residues Tyr50, His113 and Trp114 are conserved in aldose and aldehyde reductases. In the case of aldehyde reductase residues from the C-terminal loop do not form hydrogen bonds with the inhibitor Fidarestat. Leu300, a residue previously identified as essential in the determination of inhibitor potency for aldose reductase is a Pro in aldehyde reductase and can not form a hydrogen bond. Furthermore, molecular modelling calculations suggest that the conserved Trp220 may play a role in the disparity in IC_{50} values for the two enzymes. These results could provide a structural basis in the design of potent and specific inhibitors for aldose reductase.

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