Inhibitor Binding to Aldose Reductase Studied at Subatomic Resolution

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Aldose reductase (ALR2; EC 1.1.1.21), which reduces D-glucose into D-sorbitol, is believed to cause the development of severe degenerative complications of *diabetes mellitus*. Therefore, ALR2 is the target of an extended effort in inhibitor development. We have solved the X-ray structure of complexes with ALR2 and a large number of inhibitors, of which several are at atomic and subatomic resolution, with either a carboxylate head (IDD 594, 0.66 Å) or an hydantoin head (fidarestat, 0.92 Å; minalrestat, 1.10 Å). Inhibitors bind to a charged "anionic site" in the active site cleft. The structure of IDD 594 showed very precise details, with departures from standard stereochemistry, as well as hydrogen atoms and unusual contacts for a Br atom in the inhibitor. The structure of fidarestat showed the presence of Cl^- ions replacing buried water molecules in the active site. The Cl^- ion has been clearly identified in an anomalous difference map. These observations explain inhibitor binding, which is crucial for drug design.

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