Molecular Basis for Tay-Sachs Revealed by the Crystal Structure of Human β-HexosaminidaseA

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β-hexosaminidase-A (HexA) is essential for the degradation of G_{M2} glycolipids in the central and peripheral nervous system. Accumulation of G_{M2} leads to neurodegeneration associated with Tay-Sachs and Sandoff disease. Here we present the X-ray crystallographic structure of human lysosomal HexA to 3.0Å resolution. The structure reveals a heterodimer consisting of an α- and a β-subunit. The dimer interface creates two distinct active sites: and α(β) and β(α); only the α(β) site can hydrolyse G_{M2} whereas both sites can hydrolyse oligomers of NAG. We also present a second structure of HexA with a NAG-thiazoline, a transition state substrate analog, bound in the active site. Hex A, a member of Family 20 of the glycosyl hydrolases, makes use of substrate-assisted catalysis in the removal of the non-reducing sugar from an oligosaccharide. The intermediate in the reaction pathway of G_{M2} is a cyclic oxazolinium formed by the acetyl group on C2' of the non-reducing β(1,4)-GalNAc of the substrate. In both active sites, the general acid is a Glu residue and the positive charge of the oxazolinium ring is stabilized by the negative charge on an Asp residue. In the α(β) site, G_{M2} binding is promoted by Arg424 and Asn425 residues. The β(α)-site lacks these key residues but has Leu453 and Asp452 in their place that would repel the negatively charged sialic acid of G_{M2}.

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