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High Resolution Crystal Form of Human Placental D-Glyceraldehyde-3-Phosphate Dehydrogenase.
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Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) is an NAD-dependent glycolytic enzyme that catalyzes the reversible formation of 1,3-bisphosphoglycerate from glyceraldehyde-3-phosphate. Although GAPDH was once thought to play a role in glycolysis only, the mammalian protein has been implicated in many cellular activities. GAPDH appears to play a role in neurological diseases like Huntington's, Alzheimer's, and Parkinson's (PD). Apoptosis of neuronal cells is central to all three of these diseases and during apoptosis GAPDH accumulates in the nucleus. Blocking this buildup of GAPDH has been shown to slow apoptosis in some cell lines. We chose to pursue the structural determination of recombinant human placental GAPDH (HsGAPDH). A 1.75 Å resolution data set has been collected at beamline 19-ID at APS. Molecular replacement calculations were performed with the program AMoRe followed by refinement using CNS. The structure has 3 NAD⁺ bound and provides an updated view of the NAD⁺ binding site, which is the target of GAPDH inhibitors designed to combat parasitic diseases. This is the first structure of a human GAPDH that is of sufficient quality to guide drug design efforts of new PD drugs and specific inhibitors of GAPDH from protozoan parasites.