The structure of serine hydroxymethyltransferase as modeled by homology and validated by site-directed mutagenesis

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Serine hydroxymethyltransferase (SHMT: E.C. 2.1.2.1) catalyzes the reversible conversion of serine and tetrahydropteroylglutamate (H4PteGlu) to glycine and 5,10-methylene-H4PteGlu. This reaction is the major source of one-carbon groups required in the biosynthesis of methionine, choline, thymidylate, and purines. The SHMT enzyme is widely distributed in nature, and found in both prokaryotic and eukaryotic cells with the latter containing both cytosolic and mitochondrial forms. In addition to H4PteGlu, the enzyme also requires pyridoxal 5'-phosphate (PLP) as a coenzyme. It is one of a group of PLP enzymes that cleave one of the bonds at the a-carbon of their amino acid substrate. These are referred to as the _-family of PLP enzymes and include the transaminases and amino acid decarboxylases. Three-dimensional structures have been determined for several members of the _-family of vitamin B6-dependent enzymes. Amongst them are aspartate aminotransferase (AAT), tyrosine phenol-lyase (1TPL), _-amino acid aminotransferase, 2,2-dialkylglycine decarboxylase (2DKB), ornithine aminotransferase, glutamate-1-semialdehyde aminomutase, and ornithine decarboxylase (1ORD). Despite the widely differing reaction specificity and weak sequence similarity, these proteins share the same basic folding pattern which was assumed also for SHMT (2). The prolonged unavailability of the SHMT atomic structure prompted the construction of a three-dimensional "homology" model that integrated knowledge regarding the enzyme acquired through site-directed mutagenesis experiments and other experimental measures. E. coli SHMT was modelled because most of experimental data are available for this enzyme. New features of the active site are proposed for further experimental testing.