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MAPPING THE ACTIVE SITE OF EPSILON-TRIMETHYLLYSINE HYDROXYLASE

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ε-trimethyllysine hydroxylase (TMLH) is a non-heme Fe(II) and 2-oxoglutarate (2OG) dependent dioxygenase located in the submitochondrial matrix. This enzyme is crucial for the stereospecific oxidation of ε-trimethyllysine (TML) to β-hydroxytrimethyllysine (HTML), the first step in the biosynthesis of L-carnitine. It is proposed that the regulation of enzymatic activity of TMLH may have more potent cardioprotective effect than meldonium (clinically used anti-ischemia drug) that is an inhibitor of γ-butyrobetaine hydroxylase (GBBH), the final step of the L-carnitine production. Due to failure of the crystallographic methods there is still lack of information about the structure of the TMLH and especially about its active site. In this work, we applied *in silico* and *in vitro* methods to design the possible active site of TMLH. The structure of the TMLH was modeled using homology modeling approach based on the closest homolog, GBBH (used as template). However, the overall similarity between both enzymes was slightly below 30%. Thus, various modeling softwares were tested, and the resulting structures were optimized during molecular dynamics simulations. This approach gave the insights into possible enzyme fold. Next, the NMR protein-ligand binding experiments (T1ρ, waterLOGSY and ST1D) and the enzymatic assay (reaction monitored by 1D ^{1}H-NMR) revealed some crucial structure-activity relationships (SAR) that in combination with molecular docking and previous *in silico* data allowed to construct estimated active site of TMLH.

Biography

Zelencova D is a PhD student at the Riga Technical University, Latvia. She is the Research Assistant at the Latvian Institute of Organic Synthesis: NMR group.

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