Brief Abstract

The pyridoxal-5'-phosphate-dependent enzyme serine racemase (SR) is responsible for the biosynthesis of D-serine in the mammalian central nervous system. D-serine acts as a neurotransmitter and coagonist, together with L-glutamate, of ionotropic *N*-methyl-D-aspartate receptors (NMDARs). Excitotoxic D-serine levels have been implicated in neuropathologies including Alzheimer's disease and amyotrophic lateral sclerosis. SR inhibitors offer a novel and potentially highly specific approach for attenuation of NMDAR-mediated glutamate excitotoxicity and for further study of the pathway. Many of the SR inhibitors described to date are small, naturally occurring compounds, and novel structures capable of influencing SR's activity are highly sought after. Moreover, structural information about this enigmatic enzyme is lacking, and suitable animal models need to be identified for inhibitor studies.

This thesis presents the first published biochemical comparison of mouse and human SR orthologs, validating, at least in part, the use of mouse models in SR research. Additionally, hydroxamic acids are introduced as a novel class of SR inhibitors. While the experimentally determined structure of a mammalian SR remains elusive, random and site-directed mutagenesis experiments in combination with multiple sequence alignment offer insight into structure-function relationships within the enzyme.