ABSTRACT

Serine racemase (SR) is a pyridoxal-5'-phosphate-dependent enzyme responsible for biosynthesis of D-serine, a recognized neurotransmitter acting as a co-activator of N-methyl-D-aspartate (NMDA) type of glutamate receptors in the mammalian central nervous system. The hyperfunction of the mentioned receptors have been shown to be implicated in many neuropathological conditions including Alzheimer's disease, amyotrophic lateral sclerosis and epilepsy. To alleviate the symptoms of these diseases, several artificial blockers of NMDA receptors have been introduced into the clinical practice. However, many of these compounds cause undesirable side effects and it is thus necessary to search for either less harmful blockers or regulators of other targets of pharmaceutical intervention that are involved in NMDA receptor activation. In this context, specific inhibition of serine racemase seems to be a promising strategy for regulation of NMDA receptor overstimulation.

Mouse serine racemase shares 89% identity with its human ortholog and it was also shown that both enzymes possess similar kinetic parameters and inhibitor specificity. Therefore, the mouse models can be used to search for a potent human serine racemase inhibitor. Although many different compounds for their inhibitory potency towards serine racemase have been tested, no inhibitor with high binding affinity has been identified. This study aimed to build on the research performed so far and investigate whether the modifications of the most potent inhibitors of serine racemase published to date – L-*erythro*-3-hydroxyaspartate and malonate – could lead to increase of inhibitory efficiency towards the enzyme.

For this purpose, mouse serine racemase was expressed, purified and characterized. Subsequently, 50 compounds were tested for their inhibitory potency towards prepared enzyme and binding affinity and mechanism of action of the most efficient inhibitors was explored. This led to discovery of dichloromalonate as the compound with the highest binding affinity towards mouse serine racemase observed to date. Additionally, 3-hydroxyglutamates were identified as novel substrates of serine racemase side reaction activity possessing one of the best kinetic constants published to date.