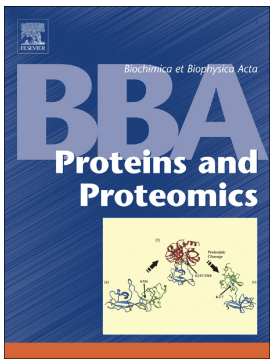

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Human D-amino acid oxidase: the inactive G183R variant

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Abstract

In the brain, the enzyme D-amino acid oxidase (DAAO) catalyzes the oxidative deamination of D-serine, a main positive modulator of the N-methyl-D-aspartate subtype of glutamate receptors (NMDAR). Dysregulation in D-serine signaling is implicated in the NMDAR dysfunctions observed in various brain diseases, such as amyotrophic lateral sclerosis, Alzheimer's disease, schizophrenia. A strain of ddY mice lacking DAAO activity due to the G181R substitution ($DAAO^{G181R}$ mice) and exhibiting increased D-serine concentration as compared to wild-type mice shows altered pain response, improved adaptative learning and cognitive functions, and larger hippocampal long-term potentiation. In past years, this mice line has been used to shed light on physiological and pathological brain functions related to NMDAR. Here, we decided to introduce the corresponding substitution in human DAAO (hDAAO). The recombinant G183R hDAAO is produced as an inactive apoprotein: the substitution alters the protein conformation that negatively affects the ability to bind the flavin cofactor in the orientation required for hydride-transfer during catalysis. At the cellular level, the overexpressed G183R hDAAO is not fully targeted to peroxisomes, forms protein