CNS-Permeable Glutamate Carboxypeptidase-II (GCPII) Inhibitors as Potential Therapeutics in the Treatment of Traumatic Brain Injury (TBI)

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Traumatic Brain Injury (TBI) is an intracranial damage common among soldiers and impact-sport athletes. In severe cases, TBI is associated with neurodegeneration and dementia if left untreated. Numerous studies have elucidated the molecular mechanisms of TBI, including the upregulation of the glutamate-carboxypeptidase-II (GCPII) enzyme. GCPII, a metalloenzyme, cleaves N-acetylaspartylglutamate (NAAG) into N-acetylaspartate (NAA) and glutamate. The upregulation of GCPII correlates with an accumulation of glutamate within the brain, causing severe neuronal damage. In-vivo studies have shown that deletion/inhibition of the GCPII enzyme reduces glutamate expression and neurodegeneration in TBI. Despite enormous efforts, no CNS-permeable inhibitors of the GCPII receptor have yet reached clinics. In this study, we performed 1) property-based enumeration of commercially available drug-like compounds to ensure CNS permeability and 2) structure-based pharmacophore modeling to identify high-affinity GCPII inhibitors. X-ray structures of GCPII-ligand complexes from the Protein Data Bank were used to generate a pharmacophore model to screen against a database of ~80,000 CNS-focused compounds. Out of twenty-five compounds with the desired features critical for high-affinity binding of GCPII, three compounds with features homologous to known inhibitors were chosen. Subsequently, molecular docking and molecular dynamics simulations were used to analyze ligands' stability and interactions within the GCPII enzyme site. Further studies are needed to assess the in vitro and in vivo efficacy of these molecules in healthy and disease models to advance to clinics. If successful, this study will result in one or more orally administered potential therapeutics for treating TBI patients.