Treating Alzheimer's Disease: New Proposal for Grayanotoxin Ligand Binding to the Carbonic Anhydrase I Receptor

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The Carbonic Anhydrase I (CA I) receptor, is involved in regulating water/pH levels. When CA I activity is elevated, CA I antagonists can potentially treat diseases like osteoporosis, epilepsy, and stroke. When CA I activity is low, CA I agonists can potentially treat problems like Alzheimer's disease and other neurodegerative diseases. Grayanotoxin III (GTX III) is an effective CA I antagonist. The ultimate goal of this project is to use the GTX III structure as a scaffold to derive an agonist to treat Alzheimer’s. Using a rational drug design approach, I developed my null hypotheses:(a) A novel allosteric site for CA I will not be identified;(b) a new molecular mechanism of action will not be identified; (c) structural modifications of the GTX III molecule will not lead to a novel small molecule that binds better than GTX III, and (d) the to the top novel CA I antagonist developed will not be more effective than Acetazolamide. Through experimentation, I discovered a potential allosteric site for CA I, named Site 1 and analyzed key characteristics that make Site 1 promising. As a result, I have proposed Site 1 as a new molecular mechanism of action for GTX III binding to CA I. Through in-silico experimentation, I designed novel antagonistic compounds that will provide a scaffold to develop agonists to treat Alzheimer’s. I further discovered that my novel antagonists have their own promising application as CA I inhibitors to potentially treat stroke, epilepsy, hypertension and osteoporosis. Through in silico and statistical validation my top novel CA I antagonist proved to be more effective than Acetazolamide, a currently in use CA I antagonist. The long-range goal of my research is to develop potential medication leads to treat Alzheimer’s disease.

Awards Won:

Third Award of $1,000

Patent and Trademark Office Society: Award scholarship of $5,000