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Design and Synthesis of Novel Allosteric Inhibitors of N-methyl-Daspartate Receptor by Virtual Screening Methods: Potential Neuroprotective Treatment for Acute Ischaemic Stroke (AIS)

Arshnous Marandi

The University of Sheffield, UK.

Abstract

Acute ischaemic stroke (AIS) is a global burden. In the UK, stroke is still one of the leading causes of death and nearly 2/3 of stroke survivors leave hospital with a disability. Effective neuroprotective drugs can meet the significant need for AIS management by protecting patients prior to a stroke insult, and aiding them in recovery. Excitatory neurotransmission conducted by the N-methyl-D-aspartate (NMDA) ionotropic glutamate receptor is essential for the development and function of the central nervous system (CNS). However, excessive stimulation of these membrane receptors has been implicated as one of the key contributors of neural injury in AIS and several other neurodegenerative diseases. Our aims are to use rational drug design and structure based virtual screening methods to design small molecule inhibitors which will target a short peptide sequence of the ligand binding domain of the NMDA receptor. This novel site was identified to bind to antibodies and protect against ischeamic stroke in rodent models. Using in silico methods we have identified compounds that interact well with the peptide sequence. Several compounds were tested for their efficacy and safety profiles in in vitro assay that induces NMDAR excitotoxicity such as LDH cytotoxicity assay using primary cortical neurons from mice. In addition, we also used the high content imaging analysis system (Columbus) to assess nuclear morphology of the cells when exposed to different concentrations of compounds in presence of the toxin. We have completed the virtual screening segment of the project, screening over ~25,000 compounds from commercial vendors and in-house libraries. We have narrowed these down to 27 compounds that interact well with the novel site of NMDAR, and tested them in our in vitro model. Three of these compounds were shown to be neuroprotective with reduction of cell death up to 10% at 1 and 10µM concentrations. These properties are useful to characterise further in the binding assay as well as in in vivo experiments to further understand the mode of action of the compounds.

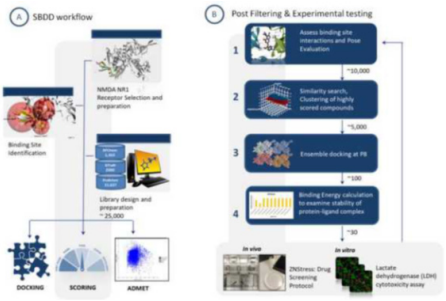

Figure 1.
Showing the work flow used throughout the project, with the structure based drug design computational work alongside the biological assay assessments.

Biography

Arshnous marandi is an associate research scientist at Afchempharm, working on a multidisciplinary PhD project with the company and department of neuroscience (SITraN) at The Sheffield University. She currently completing the final year of my PhD. The focus of her thesis is using computational docking screening and synthetic procedures to design and develop a novel antagonist for N-methyl-D-aspartate receptors (NMDAR). These receptors have been known to contribute in excitotoxicity that leads to neurodegeneration and death of brain cells. Throughout her career she hoping to provide more insight on these complex biological systems. Ultimately, hoping to contribute to developing potential therapeutics for these detrimental diseases.

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