Novel Pharmacotherapy for Treating Cognitive Dysfunction and Chronic Pain in Alzheimer’s Disease

Abhijit R. Kulkarni1, Qi Ye1, Deniz Bagdas2, Roger L. Papke3, Jonghan Kim4, M. Imad Damaj2, Ganesh A. Thakur1

1Department of Pharmaceutical Sciences, Bouvé College of Pharmacy, Northeastern University, Boston, MA, 02115, USA; 2Molecular Medicine Research Building, Virginia Commonwealth University, Richmond, Virginia, 23298, USA; 3Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL, 32610, USA;

Abstract and Background:

Alzheimer’s disease (AD) is an irreversible neurodegenerative disorder which leads to dementia and chronic pain; a combination difficult to manage, and worsens over time, completely incapacitating the individual. Current therapies modestly manage only one of these medical conditions at a time and a pharmacotherapy that addresses all the above issues without significant side effects is an unmet medical need. In the past couple of decades, α7 nicotinic acetylcholine receptor (nAChR) has emerged as a target that holds such a promise. The activation of α7 nAChRs through potent orthosteric agonists has met with limited clinical success due to lack of efficacy, off target activity and hERG inhibition. An alternative strategy is to target the allosteric site(s) on the α7 nAChRs. As allosteric sites are less conserved as compared to orthosteric sites, they significantly lack off-target activity. 4BP-TQS, an allosteric agonist- positive allosteric modulator (apo-PAM) was found to be such ligand than created the receptor on its own and enhanced the activity of the endogenous ligands (e.g. Acetylcholine). In-house microwave-accelerated synthesis of 4BP-TQS and its covalent complexation yielded GAT107 ([9] enantiomer), which was found to be the active enantiomer in electrophysiology studies in Xenopus oocytes. GAT107 was furthered into in vivo studies with various animal models of memory and chronic pain models to evaluate its efficacy. Our preliminary data strongly supports that this novel class of compounds acting through a unique mechanism (apo-PAM) provides a better approach for improving cognitive deficiencies and associated chronic pain. GAT107 will help develop novel, potent and safe α7 nAChR apo-PAMs as an effective and unique pharmacotherapy for Alzheimer’s disease.

Hypothesis

The allosteric agonism and modulation of α7 nAChR is a novel approach which helps in improving cognitive and memory impairments and alleviating chronic/ neuropathic pain in Alzheimer’s disease.

Chemistry

Using our in-house developed synthetic approach with a microwave synthesizer, we were able to synthesize the racemate 4BP-TQS using the three-component Povarov reaction, in 15 minutes at double (70%) the yield as compared to the conventional method which required 24 hrs. It was then separated into its enantiomers GAT107 (1a) and GAT107 (1b) using chiral chromatography.

Results and Methods

In vitro model:

Data shows the effectiveness of the (+) enantiomer 1b, but not 1a, as an allosteric agonist and a PAM (10μM). These effects were not affected when 1a was co-applied, suggesting that 1a is not a competitive antagonist of the active isomer. GAT107 displayed 3 types of activities - direct activation, direct potentiation and primed potentiation.

Summary

- Electrophysiological revealed that all the activity resided in the (+) enantiomer (GAT107) with 3α,4,5,6β as the absolute stereochemistry. The inactive (-) enantiomer did not affect its activity when co-applied. GAT107 has three different activities: direct activation, direct potentiation and primed potentiation.

- GAT107 was found to be effective in all the animal models of cognition and memory as well as inflammation, chronic and neuropathic pain and did not have any locomotor or hypothermic side effects.

- Our preliminary data strongly supports that this novel class of compounds acting through a unique mechanism (apo-PAM) provides a better therapeutic avenue. GAT107 is currently being optimized for the development of novel, potent and safer apo-PAMs of α7 nAChR as effective pharmacotherapy for dementia and chronic pain in Alzheimer’s disease.

References

- Gill et al., A Series of α7 Nicotinic Acetylcholine Receptor Antagonists with Close Chemical Similarity but Diverse Pharmacological Properties. Mol Pharm., 2012, 8(7);710-18
- Thakur et al., Expeditious, stereospecific resolution, and enantiomer functional characterization of 4-4-bromophenyl-5α,6,7,8-tetrahydro-3H-cyclopentooxazol-3-one -sulfonamide (4BP-TQS) an allosteric agonist-positive allosteric modulator of α7 nicotinic acetylcholine receptors. J. Med. Chem, 2011, 54(21):8948-57
- The activity of GAT107, an allosteric activator and positive modulator of α7 nicotinic acetylcholine receptors (α7nAChR), is regulated by aromatic amino acids that open the conductive interface. J. Exp. Med, 2018, 207(9):1911-29

Acknowledgements: NIDA (NIH) support through the grant # DA027113 and NIGMS support through the grant # GM057481