Galantamine for Mild to Moderate Alzheimer's Disease-Related Dementia

Poster Team: Peter Jackson, Mathew Letizia, Brian Trinh
Jmol Design Team: Brian Nguyen, Michael Vineburg, Michael Sitzman
E Poster Team: Nhan Vu, Brad Betts, Jenny Dettmer
Faculty Advisors: Daniel S. Sem, Ph.D. and Frank Dailey, Ph.D.
Professional Mentor: Bill Ross, R.Ph., Ye Olde Pharmacy
Concordia University Wisconsin School of Pharmacy, 12800 N. Lake Shore Drive, Mequon, WI 53097

Abstract

Galantamine is an acetylcholinesterase (AChE) inhibitor used as a primary treatment for Alzheimer's Disease (AD)[1]. The purpose of this poster is to analyze the mechanism of action (MOA) of galantamine at its binding site, as well as the drug-drug interaction between galantamine and tolterodine, a medication used to treat overactive bladder. We will explore these interactions on the molecular level, using Jmol images to reinforce our discussion.

Introduction

A patient who was currently taking galantamine ER 16mg capsules for AD walked into a pharmacy with a prescription for tolterodine 2mg capsules for overactive bladder. The pharmacist completed a drug utilization review for the patient's medication list, and discovered an interaction between galantamine and tolterodine.

MOA of Galantamine

- Competitively inhibits AChE, the enzyme responsible for degrading the neurotransmitter, acetylcholine (ACh), in the synaptic cleft of neurons[2]
- Accumulating ACh molecules in the synaptic cleft stimulate ACh receptors on the post-synaptic neurons in the brain[2]
- May slow the progression of deteriorating cognitive function and memory in AD which may result from a decreased amount of ACh in the synaptic clefts of the brain[3,4]

MOA of Tolterodine

- Non-specifically antagonizes ACh receptors in the urinary tract to treat overactive bladder
- By decreasing amounts of ACh, it inhibits the contraction of the detrusor muscles in the bladder and the relaxation of the urinary sphincters [5]
- This activity, however, is non-specific and can also inhibit ACh receptors in the brain [5]

Drug-Drug Interaction

- The accumulation of ACh resulting from taking galantamine can no longer bind to target receptors in the post synaptic neurons of the brain due to receptor antagonism by tolterodine [4]
- This renders the excess ACh ineffective in elucidating cognitive and protective effects

Molecular Story

Galantamine is a phenanthrene derivative (figure 1) with a tertiary amine that crosses the blood brain barrier (BBB) to exert a central cholinergic effect. The action of galantamine is also reversible, meaning that it can be displaced from its active site[1,6].

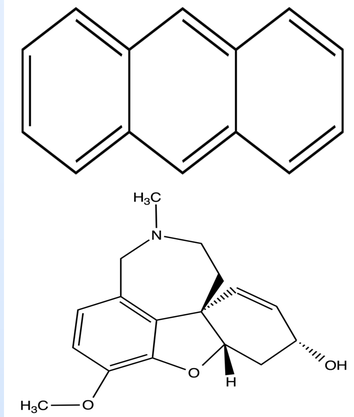

Figure 1: The chemical structures of phenanthrene (top) and galantamine (bottom). Rendered using ChemDraw.

Unlike other AChE inhibitors such as donepezil, galantamine directly interacts with Tyr337 (Y337), which is the "swinging gate" of the binding site[7]. Donepezil binds Y337 indirectly through water. Galantamine is unique in that its tertiary amine (N10) binds directly to Y337, giving it a stronger bond[8]. This interaction between tertiary amine (N10) and Y337 is shown in figure 2.

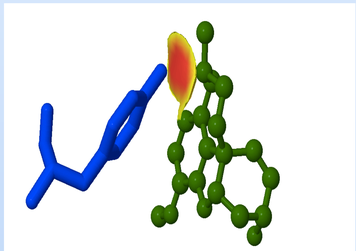

Figure 2: Galantamine (green) interacting with Y337 (blue). The orange represents the strength of the interaction. Rendered in Jmol using PDB 4EY6.pdb.

The oxygen moiety on the methoxy group of galantamine is in close proximity and binds to Ser200 and His440 of the catalytic triad in AChE (figure 3); the only catalytic residue it doesn't directly bind to is Glu327. These interactions support the ability of galantamine to inhibit the hydrolysis of ACh[9].

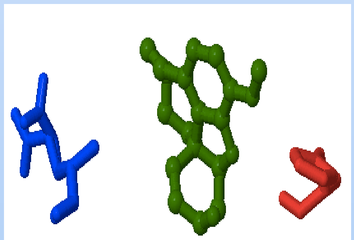

Figure 3: Galantamine (green) interacting with Ser200 (blue) and His440 (red), two of the three members of the "catalytic triad" Rendered in Jmol using PDB 4EY6.pdb.

In addition to galantamine's effect on AChE, it also binds to an allosteric site on the nicotinic acetylcholine receptor (nAChR), one of the ACh receptors in the brain. In doing so, it counteracts the effects of the damaged neurons secondary to AD without as much natural ACh activity . This potentiates the effect of galantamine in treating AD. Although this effect is clinically observed, the allosteric binding mechanism for nAChR has not been fully understood.[12]

Galantamine is an effective treatment for mild to moderate AD, given its unique structure being a naturally occurring tertiary alkaloid. It's main mechanism is exerted by:

- Binding 2 of the 3 residues in AChE's catalytic triad (SER200 and HIS440)
- Stabilized binding through interaction with Y337
- nAChR modulation

The Next Question

- Galantamine's low protein binding and its reversibility make it a good choice[10]. Unlike donepezil, its low protein binding allows it to be more dependent on blood flow rather than the amount of protein in the blood[10,11]. However, galantamine's half life is only 7 hours compared to the 70 hour half life of donepezil[10,11]. A longer half life than 7 hours for a medication used to treat Alzheimer's dementia would be preferred.
- We hypothesize that adding electron withdrawing groups to the phenyl ring could increase pi stacking interactions with Y337 by drawing electrons away from the center of the ring and in turn making the pi bond less negatively charged. This would interact with the more negatively charged phenyl group on Y337, giving it a stronger bond, which could increase both potency of binding time of galantamine, therefore increasing the half life. A proposed structure is shown in figure 4.

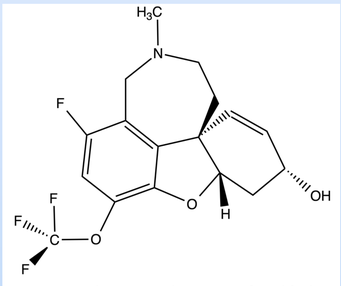

Figure 4: The proposed structure of modified galantamine. Rendered using ChemDraw.

- Further research in terms of molecular structure is needed to investigate the mechanism of allosteric up-regulation of nAChR.

For our specific patient case, there are a few options to address this interaction:

1. Switch the tolterodine to a bladder control medication with a more selective target, such as tamsulosin.
2. Increase the dose of galantamine to compensate for the greater inhibition of ACh receptors.
3. Discontinue the tolterodine altogether.

Summary

Galantamine is a competitive inhibitor of ACh, which has a unique mechanism of action compared to others such as donepezil. The biggest interactions are with the "swinging gate", Y337, as well as with Ser200 and His440, two of the three amino acids in the catalytic triad. It also interacts with nAChR in an allosteric site, but in order to determine specifics of the molecular interaction, more studies are needed.

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