Donepezil: A Patient Case Related to Medicinal Chemistry and Drug Design

Poster team: Lara Johnson, Tiffany Palm, Melodie Romanowich

Jmol design team: John Dalton, JiYoung Kim, Steve Scholzen

Faculty Advisor: Daniel S. Sem, Ph.D.

Concordia University Wisconsin School of Pharmacy, 12800 N. Lake Shore Drive, Mequon, WI 53097

Professional Mentor: Kerri Garant, RPh.

Wal-Mart Pharmacy, 825 E. Green Bay Avenue, Saukville, WI 53080

Abstract

Alzheimer's disease (AD) is a debilitating and incurable disease. While there are relatively few pharmacological treatments available for AD, donepezil and compounds like it are beneficial due to their role in increasing levels of acetylcholine in the brain which results in fewer symptoms.

Introduction

A patient came into the pharmacy to pick up a new prescription for oxybutynin 5 mg daily for the treatment of an overactive bladder. The pharmacist noticed that this patient was also taking donepezil 10 mg daily for the treatment of Alzheimer's disease (AD). These two drugs have opposing mechanisms; donepezil works to increase the levels of acetylcholine (ACh) in the body, while oxybutynin works to block the effects of ACh. This project explores the molecular interactions of donepezil binding to acetylcholinesterase (AChE) and discusses the mechanism of the drug-drug interaction with oxybutynin.

ACh is a major neurotransmitter involved in the pathophysiology of AD. A decrease in levels of ACh in the brain is thought to be involved in some of the cognitive symptoms of AD, specifically memory loss. Donepezil is a reversible AChE inhibitor, which binds to the active site of the enzyme that degrades ACh and thus prevents the hydrolysis of it. The result is an increased concentration of ACh in the synapses available for neurotransmission[1]. Figure 1 shows the alpha-7 nicotinic ACh receptor that is especially important in the cerebral cortex and hippocampus. These areas aid in the regulation of cognitive and behavioral processes[2].

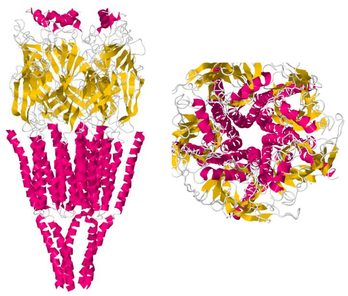

Figure 1. Nicotinic acetylcholine receptor from the side and top views[2]

Molecular Story

The structure of donepezil is made up of a dimethoxyindanone portion, a piperidine portion, and a benzyl ring, as seen in figure 2. All three segments of the molecule have specific interactions within the binding site of AChE.[3] The most important interactions are shown in figure 3.

The CREST Program is funded by grant #1022793 from NSF-CCLI.

- The benzyl ring is involved in a parallel π-π stacking interaction with the Trp84
- The piperidine ring with a charged nitrogen interacts with Phe330 and the nitrogen also forms a hydrogen bond with a water molecule
- A π-π interaction happens between the dimethoxyindanone ring and the ring of Trp279

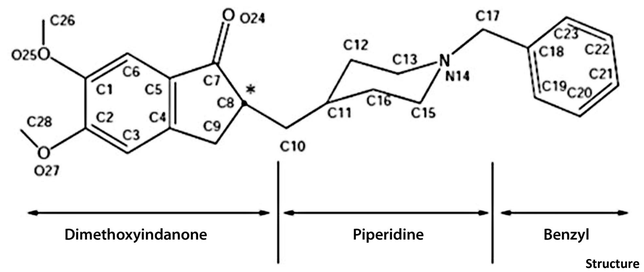

Figure 2. Structure of donepezil[3]

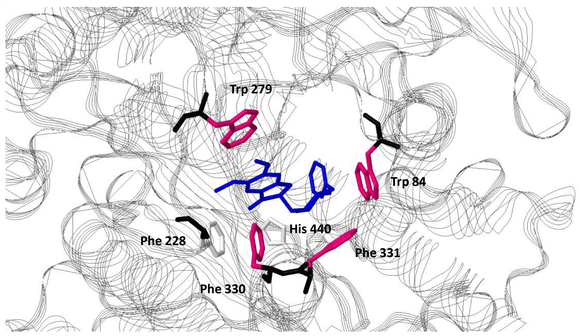

Figure 3. Donepezil (E2020) in the binding pocket of AChE. Three of the most important interactions are with Trp84, Trp279 and Phe330

Additional representations of donepezil in the binding pocket of AChE are shown in figures 4 and 5.

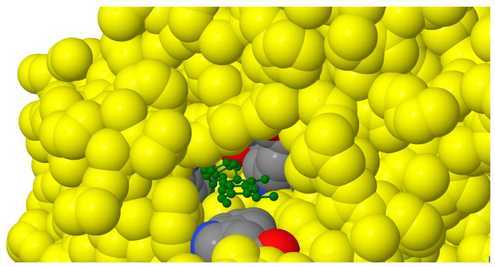

Figure 4. Close up of donepezil binding pocket with interacting amino acid residues. Carbon (gray), nitrogen (blue), and oxygen (red)

Figure 5. Ribbon structure of donepezil bound to AChE

The interaction between donepezil and oxybutynin happens indirectly. Oxybutynin is an antagonist of ACh primarily at the muscarinic receptors in the bladder.[4] Due to structural similarities of the alpha-7 nicotinic receptors involved in memory and cognition and the muscarinic receptors in the bladder, oxybutynin can bind to both. When the receptors in the brain are bound, the beneficial effects of donepezil are reduced because even though ACh concentrations are increased, there are fewer available binding sites for signal transmission.

Future Work

Despite the efficacy of donepezil in reducing symptoms of AD, there are still drug interactions and undesirable side effects such as diarrhea, nausea and muscle cramps. There are voids within the binding site that are not occupied by donepezil and could provide sites for potential modification. This may result in compounds that have even further selectivity and fewer side effects.[3] The unmodified benzyl group on the nitrogen atom of donepezil seems to be an essential requirement for the inhibitory activity of AChE. Figure 6 shows the "R" sites on the donepezil structure that may be modified by substituting ether groups, methyl groups, or other substituents. This may change how it interacts with other molecules or how it binds to the active site itself.

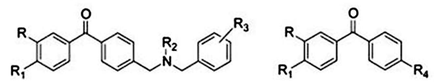

Figure 6. Molecular structure showing sites where modifications may be made[5]

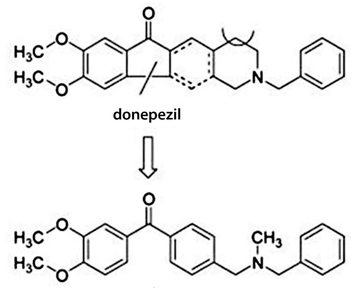

Figure 7. An example of donepezil molecular modification[5]

The addition of substituents to the donepezil backbone is shown in figure 7. The increase of steric hindrance, due to the presence of substituents may fill the active site of AChE better than the original structure of donepezil to decrease side effects and interactions.

Summary

Donepezil inhibits AChE, leading to more available ACh and improved cognitive functioning. Although donepezil has an important place in AD therapy, there are still some disadvantageous side effects and drug interactions. Modification of the structure of donepezil is the next step to creating a drug with fewer negative effects and greater potency.

References

1. Atri A, Chang MS, Strichartz GR. Cholinergic Pharmacology. In: Golan DE, Tashjian AH, Armstrong EJ, Artmstrong AW, editors. Principles of pharmacology. Baltimore: Lippincott Williams & Wilkins; 2008. p. 104-120.
2. Unwin N. Refined structure of the nicotinic acetylcholine receptor at 4A resolution. J Mol Biol. 2005 Mar 4;346(4):967-89.
3. Kryger G, Silman I, Sussman JL. Structure of acetyl cholinesterase complexed with E2020 (Aricept): imp lications for the design of new anti-Alzheimer drugs. Structure. 1999 Mar 15;7(3):297-307. PDB ID: 2BG9
4. Oxybutynin hydrochloride. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically. Accessed December 5, 2011.
5. Belluti F, Piazzi L, Bisi A, Gobbi S, Bartolini M, Cavalli A, Valenti P, Rampa A. Design, synthesis, and evaluation of benzophenone derivatives as novel acetyl cholinesterase inhibitors. Eur J Med Chem. 2009 Mar;44(3):1341-8