Varenicline and the α4β2 Nicotinic Acetylcholine Receptor

Poster team: Karena Creten, Elizabeth Everett, Sirr Grice, Margaret Roesser
Jmol team: Joseph Holewa, Veronica Juarez, Thomas Puerzer, Jacob Sutherland
Institution: Concordia University Wisconsin – School of Pharmacy (CUW SOP) 12800 N Lakeshore Drive Mequon, WI 53097

Educators: Dr. D Sem, Dr. F Dailey, Dr. E Stremski of CUW SOP and Dr. M Franzen of MSOE
Professional Mentors: Amy Burton PharmD of VA Medical Center Milwaukee, WI;
Catherin Zielinski, PharmD of Pick N' Save Pharmacy Mequon, WI; Theodore Heun, RPh of Pick N' Save Pharmacy Glendale, WI.

Abstract

The addictive nature of nicotine is in part due to its high affinity for α4β2 neuronal nicotinic acetylcholine receptors (nAChR), which causes dopamine release in the brain producing the "reward" feeling of smoking. Varenicline, brand name Chantix ®, is a partial agonist of the α4β2 nAChR (1). Analyzing the binding patterns of Varenicline to the receptor helps to understand the effectiveness of the drug in smoking cessation therapy. Varenicline and nicotine have similar molecular recognition involving water acting as a bridge within the binding pocket of the nAChR. Binding of a substrate to the 5 subunits of the nAChR causes a conformational change opening the pore of the receptor. Nicotine is a full agonist to the receptor while varenicline is a partial agonist. When the pore opens it allows ions into the nerve cell, which leads to depolarization, and release of dopamine. Varenicline relieves the craving and withdrawal symptoms because it releases some dopamine while simultaneously blocking the effects of nicotine by occupying the binding site; thus allowing patients to continue smoking during therapy, while simultaneously removing the "reward" that nicotine causes.

Introduction

A 32-year-old male presented to a pharmacy with the intent to quit smoking. He unsuccessfully attempted to quit approximately 3-4 years ago. He used nicotine replacement patches but did not seek help from a health care professional. He is interested in Chantix ®.

- Nicotine replacement products have been the standard of care for many years.
- Varenicline could prove to be advantageous over agents by its unique mechanism of action.
- Varenicline is a partial agonist to α4β2 neuronal nicotinic acetylcholine receptors. (1)
- Nicotine binds to nicotinic acetylcholine receptors (nAChRs) which are pentameric members of the superfamily of transmembrane ligand-gated ion channels. (2)
- Research has shown that nicotine has an affinity to binding to the α4β2 subtype of the nAChR.
- Varenicline is a partial agonist at the α4β2 nicotinic acetylcholine receptor and binds with subnanomolar affinity and high selectivity to the receptor.
- Varenicline also antagonizes nicotine, reducing its effect by 34%. (2) Due to this antagonistic effect patients can continue to smoke while beginning the medication and taper off their smoking gradually.
- Varenicline is approximately 92% excreted from the body in its original form. (2) Thus the drug is not metabolized by Cytochrome P450 and does not interact with any medications that are metabolized by the system.
- Varenicline can produce a few side effects including nausea, insomnia and abnormal dreams. Nausea was reported to be the greatest side effect in the first couple weeks of administration and declined thereafter. (3)

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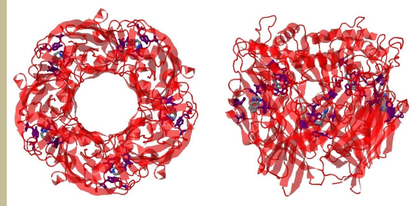
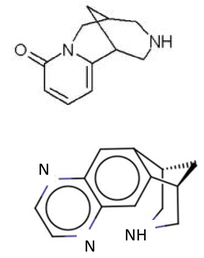
Molecular Story

1. Smoking causes 443,000 deaths annually and health care costs up to $193 billion a year. (1) So why aren't more people quitting smoking? Nicotine addiction is a difficult habit to break.

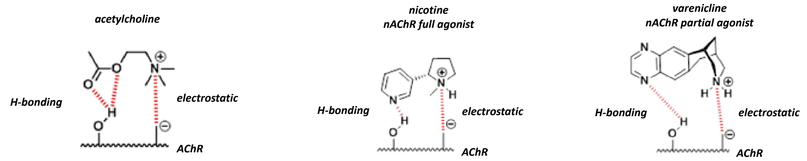
2. Nicotine binds to the α4β2 nicotinic acetylcholine receptor (nAChR) shown below from two perspectives. The receptor has 5 subunits and is a transmembrane ion channel. [created from PDB file 4AFG using jmol software] (4)



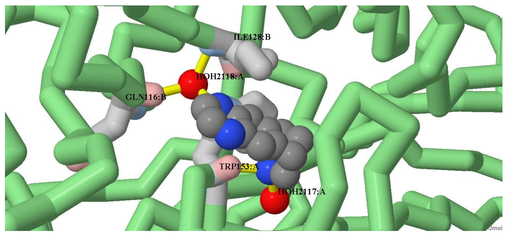
3. Cytisine (top) is a naturally occurring compound known to be a partial agonist for the α4β2 nAChR. Varenicline (bottom) is a structural derivative of cytisine. (5)



4. Acetylcholine, nicotine, and varenicline share a similar pharmacophore for bonding with the α4β2 nicotinic acetylcholine receptor. Notice that varenicline has a larger space between the two bond locations than nicotine or acetylcholine. This may explain when varenicline is a partial agonist while nicotine is a full agonist. (6,7)

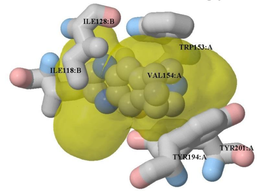


5a. Water molecules aide in the stabilization of Varenicline in the binding pocket via the formation of bridged hydrogen bonds. (7, 8) One of these bridges is formed between the nitrogen of the benzazepine ring of Varenicline and the carbonyl oxygen of TRP153 (tryptophan).

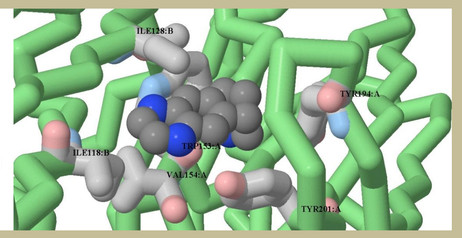


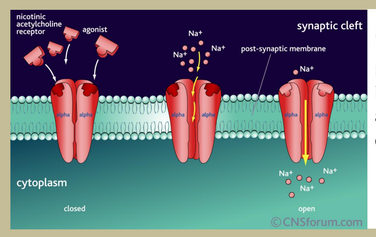
In the figure above the carbonyl oxygen (pink) of tryptophan (TRP153:A) is connected to the nitrogen (blue) of Varenicline (grey) via a hydrogen bond (yellow). The A and B after the colon refer to the different subunits of the receptor. [created from PDB file 4AFG using jmol software] (4)

5b. Varenicline within the binding pocket of nAChBP with nearby amino acids. ILE118B and ILE128B are two important amino acids that interact with Varenicline via hydrophobic interactions, while the aromatic ring of TRP153A plays a key role in the stabilization of Varenicline via cation-pi interactions. [created from PDB file 4AFG using jmol software] (4)



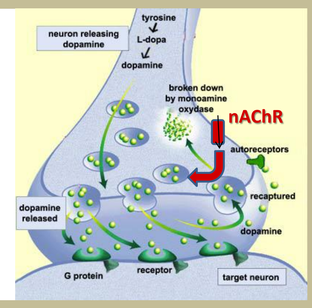
5c. Hydrophobic interactions between nAChBP and Varenicline. [created from PDB file 4AFG using jmol software] (4)





6. Binding of a substrate to the subunits of the nAChR causes a conformational change opening the pore of the receptor. The figure to the left shows a transmembrane ligand-gated acetylcholine receptor in the opened and closed states. Nicotine, like acetylcholine, is a full agonist and varenicline is a partial agonist. A partial agonist will open the channels less frequently than a full agonist. Opening of the channel leads to influx of ions and depolarization of the cell. (9)

7. Stimulation of nAChR by nicotine or varenicline leads to a depolarization of the nerve which leads to merging of dopamine filled vesicles with the cell membrane and release of dopamine into the synaptic cleft. (10)



Future Direction

Recently the FDA has mandated that Chantix® carry a black box warning that informs patients that use of this medication could potentially lead to suicidal thought and an increase in depression. This pharmacological trait could greatly decrease the number of patients that could potentially be helped by this medication. Chantix® both helps decrease the urge for nicotine as well as the craving which can occur with a decrease in dopamine release. This change in the patient's dopamine levels may play a role in the recent black box warning. Further research on the effect that dopamine plays in depression and quantify the levels of the dopamine needed to induce a depressed state for a majority of patients is needed. With improved understanding of dopamine values Chantix ® may be improved to address the side effect and become a better smoking cessation alternative for patients diagnosed with depression.

Possible ways to improve the drug design to change the amount of dopamine released: (refer to figure 4 for pharmacophore)

- By decreasing the space between the two bonding groups or removing the entire central ring of the drug, the affinity for the binding site may be improved and allow for an increase in potential dopamine release.
- Adding a polar group to an area that is not involved in the pharmacophore of the drug may improve the drug penetration into the CNS which may also increase the potential dopamine release by the drug.

Summary

Varenicline (Chantix®) shares the pharmacophore common to nicotine and acetylcholine, but has decreased efficacy due to conformational constraints of the molecule. Using Varenicline as a smoking cessation tool is useful because it helps patients with craving and withdrawal symptoms while breaking the addiction to nicotine. Further studies need to be conducted to determine the mechanism of Varenicline's off target neuropsychiatric side effects.

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