Nortriptyline: Interactions with the Dopamine Channel and the Human hERG Channel

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Abstract

Depression and anxiety disorders are very common mental illnesses, affecting about 10-15% of the population throughout their lives[1]. Nortriptyline has been used to treat depression for many years, but it has a side effect of increased risk of cardiotoxicity. Binding of nortriptyline to the hERG channel is most likely the cause of these side effects. The focus of the project is to understand the binding of Nortriptyline to the hERG channel and look for ways to prevent binding.

Case Study

A 41 year old female presented to hospital with symptoms of pneumonia. Upon diagnostic confirmation, she was initiated on sulfamethoxazole/trimethoprim 1200mg/240mg oral tablet(s) three times daily. Reviewing the patient's home medications, nortriptyline for the treatment of depression was found. Concurrent use of nortriptyline and sulfamethoxazole/trimethoprim increases the risk of cardiotoxicity, such as QTc prolongation, torsades de pointes, or cardiac arrest. The prescribing hospital physician confirmed his awareness of the interaction between the drugs and mandated their continuation with increased, careful monitoring.

Introduction

Nortriptyline[2]

- Approved for depression by the FDA in 1964
- Tricyclic antidepressant class
- Inhibits the reuptake of monoamines, such as serotonin and norepinephrine, at the synaptic junction
- This increases the concentration of monoamines in the brain, which increases neuron activation
- Off-label uses include bulimia nervosa, diabetic neuropathy, and irritable bowel syndrome

Figure 1. Teva brand Nortriptyline 25 mg[3]

In the case of our patient[4]

- Nortriptyline has an off-target effect of binding to the human Ether-à-go-go-Related Gene (hERG) channel in cardiac cells
- hERG is the potassium channel that is needed for repolarization of cardiac cells
- Binding of Nortriptyline to hERG channel can cause QTc prolongation
- QTc prolongation delays the beating of the heart and can lead to other deadly manifestations such as Torsades de Pointes
- Binding of Nortriptyline to the hERG channel is an undesirable effect. Knowing more about what causes it and how to avoid it is essential

Molecular Story

Nortriptyline[5]

- Cycloheptane with two benzene rings attached on sides (Tricyclic ring)
- Positively ionizable nitrogen (Secondary Amine)

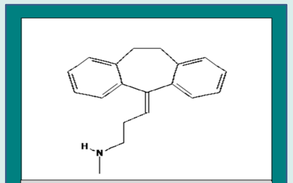

Figure 2. Structure of Nortriptyline[6]

Drug Targets[5]

- SERT - Serotonin Transporter (5-hydroxytryptamine or 5-HT Transporter)
- NET - Norepinephrine Transporter

How Nortriptyline Functions[5]

- Inhibits reuptake of SERT and NET transporters at the synaptic junction to increase the concentration of monoamines in the brain and increase neuron activation
- Non-selective due to its "privileged structure." A structural motif that fulfills several pharmacophores at once and results in many off-target effects. Nortriptyline's pharmacophore is seen in the ligands for many different channels, such as SERT, NET, dopamine, and hERG channels

How Nortriptyline Binds[5]

- The dopamine channel in the Drosophila fly was found to have over 50% sequence identity with human SERT and NET. Due to the close resemblance, interactions between nortriptyline and the Drosophila dopamine channel can be assumed to be very similar to those of the human SERT and NET
- Amino acids that are important for the binding of nortriptyline to the dopamine channel: tyrosine (Tyr124A), phenylalanine (Phe325A), and phenylalanine (Phe43A)

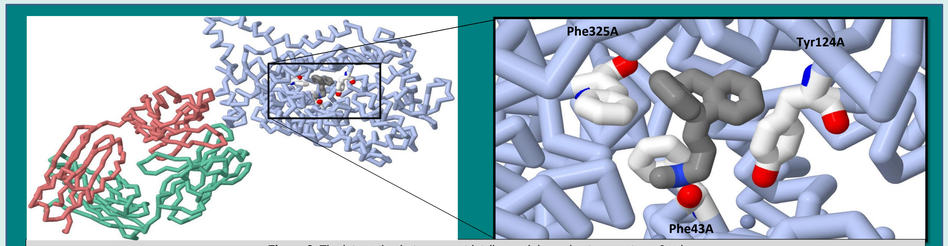

Figure 3. The interaction between nortriptyline and dopamine transporter - Jmol
Dopamine transporter is large and shown in light blue/pink/green. Nortriptyline structure shown as grey base. Dopamine side-chain binding pocket structures shown as white base. Grey/White show Carbons. Red show Alcohols. Dark Blue show Amines.

- 1st Interaction: Polar region of nortriptyline (secondary amine group) interacts with Phe43A. One hydrogen on the secondary amine group interacts with the carbonyl backbone of Phe43A. A second hydrogen on the secondary amine binds to the phenyl ring in Phe43A via pi-cation interaction that occurs within the phenyl ring
- 2nd Interaction: Non-polar region of nortriptyline (two phenylalanine side chains) interacts with two outer rings of nortriptyline. This stabilizes nortriptyline in a hydrophobic pocket and allows for a stronger bond between nortriptyline and the dopamine transporter

hERG Channel - human Ether-à-go-go-Related Gene Channel[7]

- Off-target binding site: Nortriptyline binds the hERG receptor, blocks the channel, and slows electrical conduction required for the contractility of the heart
- This induces delayed repolarization of the heart
- It is hypothesized that the pharmacophore for a hERG channel blocker contains three hydrophobic features and one positively ionizable feature with each group being 4.5 to 7.0Å of each other. This is seen in nortriptyline's structure
- Amino acids on hERG channel that interact with nortriptyline: Threonine (Thr623), Serine (Ser624), Tyrosine (Tyr652), and Phenylalanine (Phe656)
- It is proposed that Thr623, Ser624, and Phe656 interact with the polar hydrophobic regions. Tyr 652 interacts with the nitrogen via pi-stacking

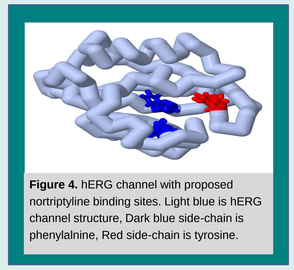

Figure 4. hERG channel with proposed nortriptyline binding sites. Light blue is hERG channel structure, Dark blue side-chain is phenylalnine, Red side-chain is tyrosine.

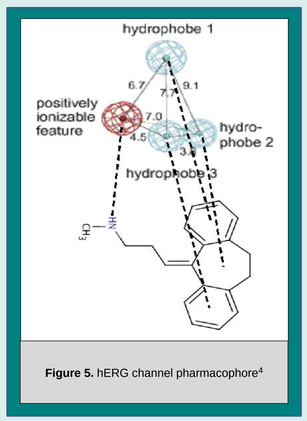

Figure 5. hERG channel pharmacophore[4]

The Next Question

To remove the QTc prolonging characteristic of nortriptyline, chemical modifications to the structure of nortriptyline are needed. Studies have shown that the hydrophobic features and the positively ionizable feature of the drug have to be within a proximity of 4.5 to 7.0 Å of each other in order for binding to the hERG channel[7].

Therefore, adding a few carbons to increase the distance between the amine group and the fused tricyclic rings to more than 7.0 Å would push nortriptyline out of the binding pocket and prevent it from binding to hERG while still retaining its ability to affect the NET and SERT.

Improvements to the structure of nortriptyline should not alter the tricyclic rings and secondary amine.

Summary

Although nortriptyline is no longer first-line therapy for depression, certain patient populations still take this medication routinely.

In viewing the drug therapy problem and undesirable effects of nortriptyline binding to the hERG receptor, alteration of the chemical structure of antidepressants would eliminate the binding to this receptor and decrease inadvertent cardiac effects.

Pharmacists play an essential role in pharmacotherapy monitoring in terms of QTc prolongation potential. Pharmacists must evaluate the risks and benefits because there currently is no hard cut off for QTc prolongation and must be available to properly educate our patients.

These duties are critical in order to minimize the potential for fatal cardiac arrhythmias, such as Torsades de Pointes, while on nortriptyline.

References

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The CREST Program is funded by NSF-DUE grants #1022793 and #1323414.