Tadalafil and its Molecular Interaction with Phosphodiesterase 5

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Abstract

Erectile dysfunction (ED) is defined as “the inability to achieve and/or maintain a penile erection sufficient for sexual performance.”[1] ED can be treated with a phosphodiesterase-5 (PDE-5) inhibitor such as tadalafil (Cialis). Patients taking tadalafil need to be cautious due to a potential drug-drug interaction with nitroglycerin, commonly taken for chest pain. This interaction can lead to severe hypotension, syncope, angina or even death.[1]

Introduction

A 58 year old male with history of ED and angina was admitted to the hospital with a bacterial infection. Home medications included tadalafil 10mg as needed for ED and nitroglycerin 0.4mg sublingual tablets as needed for angina. The pharmacist reviewing the profile talked to the patient to see if he ever takes these medications together.

PDE-5 Enzyme

- Protein is a dimer
- Principle cGMP hydrolyzing enzyme in the corpus cavernosum tissue
- Also found in lungs and systemic vasculature
- Catalyzes the degradation of cGMP, allowing for return of penile flaccidity[2]

Tadalafil

- Considered first-line treatment for ED
- A phosphodiesterase 5 inhibitor (Fig. 1)
- Enhances the effects of nitric oxide (NO) by inhibiting PDE-5 enzyme from degrading cGMP[3]
- Competitive antagonist for active site of cGMP[4]
- Binds to PDE-5 with a Kd range of 0.9-6.7 nM, approximately 200-700 times more tightly than it binds to PDE-6[5]

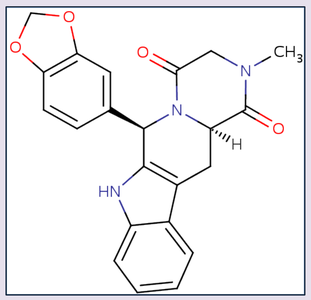

Fig. 1 Chemical structure of tadalafil.
Obtained from: http://www.drugbank.ca/drugs/DB00820

Molecular Story

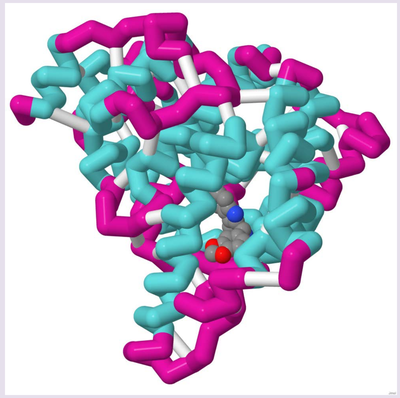

Fig. 2 Two domains of PDE-5 enzyme with alpha helices highlighted in teal and tadalafil bound in active site. Rendered from 1UDU.pdb

PDE-5 Enzyme[5]

- Composed of 2 domains: Catalytic and Regulatory (Figure 2)
- Catalytic domain contains core of 16 alpha-helices and three subdomains:
  - N-terminal cyclin-fold region
  - Linker region
  - C-terminal helical bundle
- Active site found within catalytic domain at center of C-terminal helical bundle domain

Substrate Pocket[5]

- Hydrophobic pocket approximately 10 Ångströms deep
- It is composed of four subsites:
  - Metal-binding domain (M site)
  - Core pocket (Q pocket)
  - Hydrophobic pocket (H pocket)
  - Lid region (L region)
- Tadalafil interacts most significantly with the Q and H pockets.

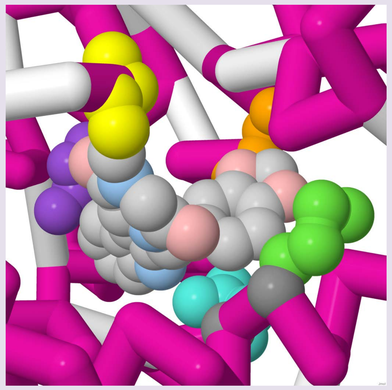

Fig. 3 Q pocket with highlighted amino acids: Alanine (orange); Tyrosine (purple); Glutamine (teal); Methionine (green); Serine (yellow) Rendered from 1UDU.pdb

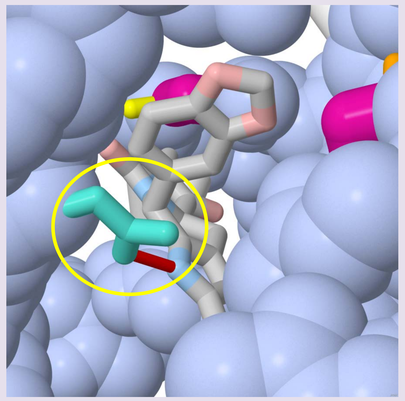

Fig. 4 Q pocket featuring glutamine interaction with hydrogen bond highlighted in red. Rendered from 1UDU.pdb

Q Pocket[5]

- Contains an alanine, tyrosine, glutamine, methionine and serine (Figure 3)
- Glutamine side chain forms a single hydrogen bond with the NH group of the indole ring of tadalafil (Figure 4)

H Pocket[5]

- Responsible for hydrophobic interactions with methylene-dioxyphenyl group of tadalafil (Figure 5)
  - May be why tadalafil maintains high affinity with PDE-5[4]

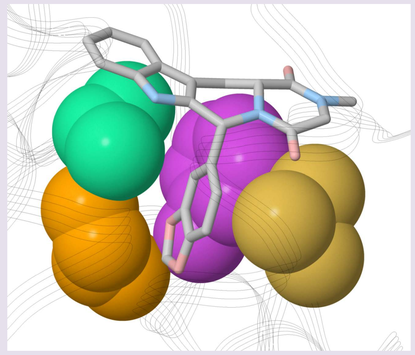

Fig. 5 H pocket of PDE-5 with tadalafil bound. Highlight amino acids: Alanine (orange); Tyrosine (purple), Glutamine (teal), Serine (yellow) Rendered from 1UDU.pdb

Future Research

One of the major side effects of tadalafil is hypotension. Patients taking tadalafil may experience symptoms including dizziness, lightheadedness, or syncope. An area of possible future research regarding tadalafil could include finding a way to limit the systemic hypotensive effect on the vasculature. Finding a way to target a specific subset of the PDE-5 enzyme could result in seeing effects only on the smooth muscle of the corpus cavernosum of the penis, thus, eliminating the systemic hypotensive effects of the drug.

Another area of future research could be finding a way to make the drug work without being a CYP 450 enzyme substrate.

Summary

Tadalafil is a medication used to treat erectile dysfunction, which works by inhibiting the PDE-5 enzyme. The PDE-5 enzyme is a protein dimer that functions to catalyze the degradation of cGMP, allowing for the return of penile flaccidity. Tadalafil inhibits PDE-5 by binding in the active site. This substrate pocket is composed of four subsites. Tadalafil interacts most significantly with the Q and H subsites.

Since PDE-5 is found in other areas of the body, patients taking tadalfil should be cautious when using nitroglycerin because it can lead to severe hypotension, syncope, angina or even death. In our case, the patient was advised to never take tadalafil and nitroglycerin together. [6]

References

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