Sildenafil (Viagra) – A Patient Case Related to Medicinal Chemistry and Drug Design

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Abstract

Erectile dysfunction (ED) is the failure to attain or maintain an erection of adequate duration and firmness to complete intercourse. Roughly 35% of American men between 40 to 70 years of age are affected by ED. Oral medications are first line therapy; several classes of drugs can treat ED including phosphodiesterase type 5 (PDE-5) inhibitors, such as sildenafil (Viagra). PDE-5 is a monomeric protein that forms a dimer to catalyze the breakdown of cGMP. Sildenafil inhibits PDE-5 in the corpus cavernosum, which increases cGMP leading to smooth muscle relaxation and vasodilation.

Introduction

AT presented to the emergency department after passing out in his hotel room. His past medical history revealed that he has been on sublingual nitroglycerin for 2 years post myocardial infarction. His wife told the admitting nurse that he just received three Viagra (sildenafil) 50mg tablets from his friend. He took the Viagra along with nitroglycerin. He passed out from excessive vasodilation and the resultant drop in blood pressure from the drug combination (1,2).

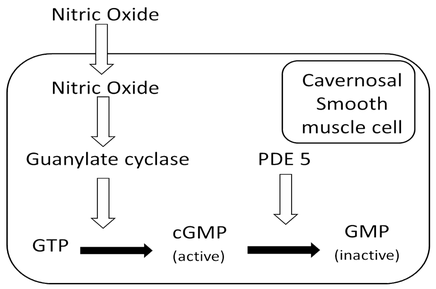


Figure 1: Mechanism of action of PDE5 Inhibitors. (3)

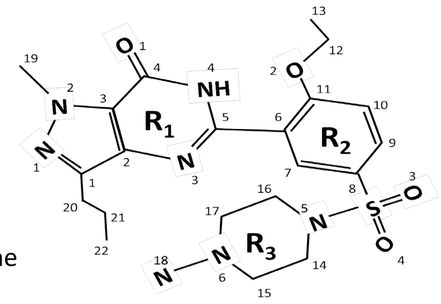
The body's main pathway for signaling vasodilation is the NO-sGC-cGMP pathway shown in Figure 1. In this pathway: NO signals for an increase in intracellular cGMP which causes vasodilation. Phosphodiesterase enzymes break down cGMP causing vasoconstriction. Drugs target this pathway via several mechanisms including: NO donors, organic nitrates, and PDE inhibitors such as sildenafil and tadalafil (4,5). Sildenafil, or Viagra, was originally designed to treat coronary artery disease (CAD) (1). This drug is now the number one prescribed treatment for erectile dysfunction. Sildenafil inhibits PDE-5, which prolongs cGMP action, and causes vasodilation. Sildenafil has some serious drug-drug interactions with other vasodilators, such as nitroglycerin and nitrates, which lead to extreme hypotension.

Molecular Story

Sildenafil is composed of three regions (Figure 2):

- R1 – pyrazolopyrimidinone group
- R2 – ethoxyphenyl group
- R3 – methylpiperazine

The R1 group is responsible for the binding affinity of sildenafil to PDE-5. Sildenafil's R1 structure is similar to the purine region on the cGMP molecule. This region is what allows the sildenafil ligand to bind into the active site in the PDE-5 protein (6).



Sildenafil

Figure 2: The letters R1-R3 label the main groups in sildenafil. R1 represents the pyrazolopyrimidnone group, R2 is the ethoxyphenol, and R3 is the methylpiperazine. *(6)*

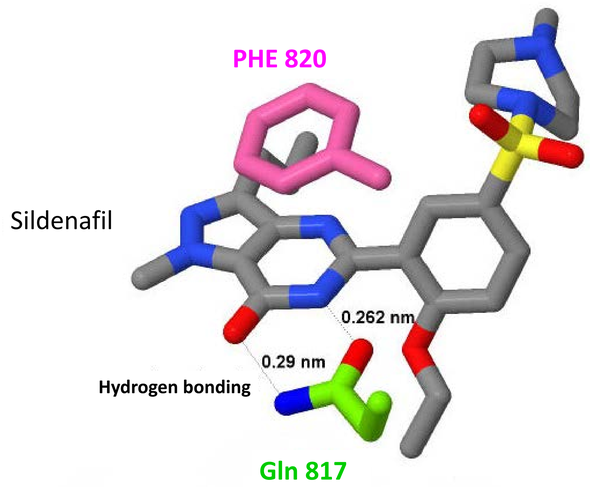


Figure 3: Sildenafil shown in the binding pocket of PDE5. The essential interactions occur with Gln817 and Phe820. Jmol image.

Sildenafil binds to PDE-5 through many interactions (Figure 3):

- Two hydrogen bonds between a nitrogen atom and an oxygen atom on Gln817 of PDE-5 and an oxygen atom and a nitrogen atom on the R1 segment of sildenafil.
- This portion of the drug is also stabilized by the stacking of a different amino acid, Phe820.
- All three segments of the drug are involved in Van der Waals' contacts and regions of hydrophobic stability (6).

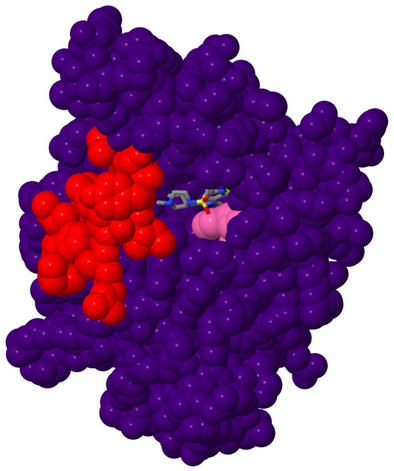


Figure 4: H-loop (red) section of PDE-5 protein (purple) closes off binding pocket after sildenafil binds. Jmol Image.

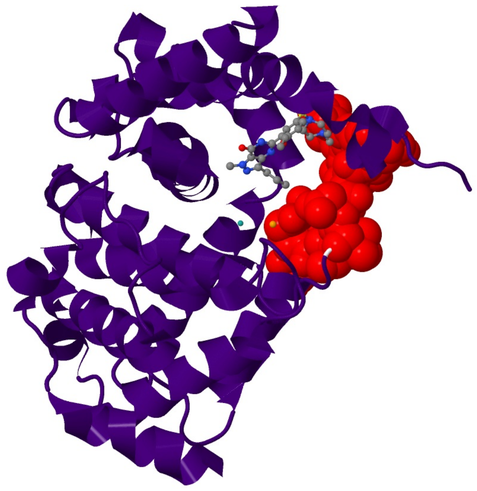


Figure 5: Close-up of sildenafil in the binding pocket. H-loop (red), magnesium (orange), zinc (light blue) and Gln659 (white). Jmol Image.

Sildenafil works by triggering the H-Loop (red section, Figure 4) to shift over the binding site rendering the PDE-5 protein inactive, unable to breakdown cGMP. The H-loop – R3 region interaction is unknown; future work to study this region of sildenafil is needed. The shift can be as great as 24 angstroms from the unbound protein. The amino acid Gln659 sits just before the H-loop and likely acts as a hinge (Figure 5) (6). There is rotation around some of the bonds in sildenafil, leading to some flexibility. Evidence suggests it can exist in three main positions. Each of these positions keep R1 and R2 constant, with rotation of the R3 region.

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Future Work

The R3 region interacts with the H-loop. More research is needed to determine three factors which will allow for a more specific description of the molecular interaction between sildenafil and PDE-5.

- Establish which of the three conformations of sildenafil is active or most active.
- Find out the position of the H-loop within the protein.
- Determine how the sildenafil ligand sits in the binding pocket and which amino acids on the H-loop the R3 region interacts with specifically(6).

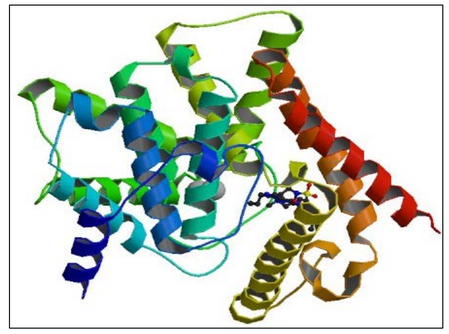

Figure 6: Ribbon structure with rainbow coloration of PDE-5 bound to sildenafil. (6)

Summary

Sildenafil inhibits PDE-5 in the corpus cavernosum, which allows more cGMP to be available leading to smooth muscle relaxation and vasodilation. This effect can compound with nitrates yielding an undesirable adverse effect. Further research is needed to see if there is an allosteric site the drug could bind to on PDE-5 in hopes of merely dampening the effect of inhibition instead of just stopping the metabolism of nitric oxide.

References

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