How Penicillin Kills Bacteria (and How Bacteria Fight Back)

Audra Amasino, Dianna Amasino, Re-I Chin, Axel Glaubitz, Hsien-Yu Shih, Xiao Zhu
Madison West High School, Madison, WI 53726
Advisor: Basudeb Bhattacharyya, University of Wisconsin, Madison, WI 53706
Mentor: Dr. Dave Nelson, University of Wisconsin, Madison, WI 53706

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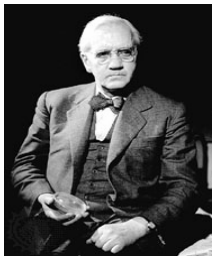


Figure 1. Discovery of Penicillin Alexander Fleming discovered penicillin in 1928

Introduction

Prior to World War II, having a bacterial infection would most likely lead to death. Drugs were needed to combat bacterial infections, especially during the war. After Alexander Fleming (Figure 1) accidental discovered penicillin in 1928 penicillin dramatically decreased the number of deaths and amputations caused by bacterial infection. Dorothy Crowfoot Hodgkins (Figure 2) solved its structure.

Penicillin is an effective drug to combat bacterial infections because it targets bacteria-specific proteins and has no effect on human proteins. When a bacterium divides, penicillin prevents it from reforming a new cell wall, and the two daughter cells "pop". However, penicillin does not combat all types of bacterial infections; it is most effective against gram-positive bacteria.

We are using RP-Rasmol to model the interaction between penicillin and pencillin binding protein 4 (PBP4-Figure 3). By understanding the interaction, creating new and improved antibiotics will be possible.

Structure of Penicillin

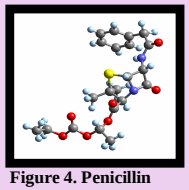
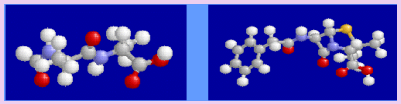


Figure 4. Penicillin

Penicillin (represented by Figure 4) is a class of drugs with a characteristic ring (β-lactam ring). Penicillin inhibits its target protein by mimicking D-alanine-alanine as shown below (Figure 5): compare the placement of oxygens and nitrogens.



D-alanine-alanine Penicillin

Figure 5. Comparison of Penicillin and D-alanine-alanine

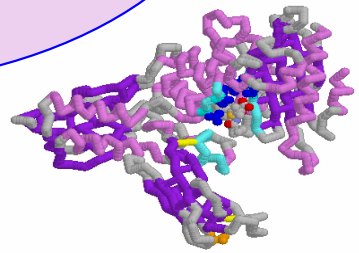


Figure 3. Penicillin Bound to Penicillin Binding Protein 4 (PBP4) Penicillin (shown in the center of the protein as CPK and ball and stick format) acts on a group of proteins (in this case, PBP4) that help form new bacterial cell walls

Bacterial Cell Wall Synthesis

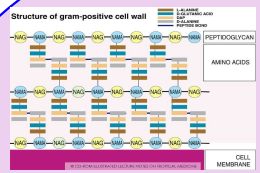


Figure 6. The Bacterial Cell Wall

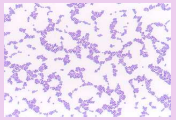


Figure 7. Gram Positive Stain

- Shown at left (Figure 6) is the peptidoglycan layer of a Gram-positive bacterium's cell wall. NAG stands for N-acetylglucosamine and NAM stands for N-acetylmuramic acid.
- When the bacteria divides, it must temporarily create "holes" in its cell wall to allow for growth and separation of the daughter cells. The "holes" are then filled in with freshly synthesized peptidoglycans.
- Bacteria are divided into two groups, Gram-positive (Figure 7) and Gram-negative, based on their cell wall formation and staining properties. Penicillin is effective only against Gram-positive bacteria because Gram negative bacteria have a lipopolysaccharide and protein layer that surrounds the peptidoglygan layer of the cell wall, preventing penicillin from attacking.

Penicillin Resistance

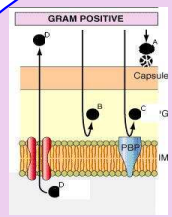


Figure 9. Penicillin Resistance

- Bacteria become resistant to penicillin in multiple ways (Figure 9)
- Sometimes bacteria develop enzymes (penicillinases-9A) which can degrade penicillin. They can then transfer this ability to other bacteria through conjugation (Figure 10). The gene for the penicillinase gets integrated into a plasmid (a circular piece of DNA), and then the bacteria can transfer the plasmid through a sex pili.
- Bacteria can also alter their peptidoglycan layer (9B) or their penicillin binding proteins (9C).
- Lastly, bacteria can develop systems to export penicillin (9D).

Figure 10. Bacterial Conjugation

Mode of Action of Penicillin

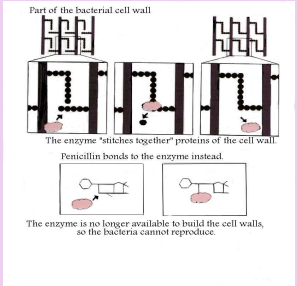


Figure 8. Penicillin Blocks Cell Wall Synthesis

- Penicillin kills bacteria by inhibiting the proteins which cross-link peptidoglycans in the cell wall (Figure 8).
- When a bacterium divides in the presence of penicillin, it cannot fill in the "holes" left in its cell wall.
- The bacterium is so filled with solutes compared to the surrounding solution that the water rushes in, and without a full cell wall to support the bacterium, it "pops" from the turgor pressure.

Figure 2.-Discovery of the Structure of Penicillin Dorothy Crowfoot Hodgkins crystallized and determined the structure of penicillin in the early 1940's, allowing for penicillin to be easily synthesized for the treatment of bacterial infections

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