

Antibiotics

The history of antibiotics

In 1928, Alexander Fleming, a Scottish bacteriologist, was studying the relationship between colony morphology of *Staphylococcus* and their virulence, he inoculated culture plates with *Staphylococcus* colonies. After two weeks, he found several cultures contaminated with *Pencillium notatum* whose presence seemed to be influencing the morphology of the surrounding *Staphylococcus* colonies, colonies in proximity to the mold were transparent and seemed to be undergoing lysis. This observation led him to realize the mold contained a microbial antagonistic property.

The term antibiosis, meaning ‘against life’ was introduced by the French bacteriologist Jean Paul Vuillemin as a descriptive name of the phenomenon exhibited by early antibacterial drugs. Antibiosis was first described in 1877 in bacteria when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of *Bacillus anthracis*.

Fleming, together with his assistants, set out to purify the lytic agent, which he dubbed ‘penicillin’ released into the broth by the mold. Serial dilutions of these extracts inhibited growth of *Staphylococci*, *Streptococci* and *Pneumococcus* cultures.

In 1940, Florey, Chain and eight coworkers reported successful use of penicillin to cure infections in mice, rats and cats, a year later the first clinical use of penicillin in 10 human subjects suffering from *Staphylococcus aureus* infection was described.

Selman, A. Waksman, soil microbiologist introduced the term antibiotic in 1942, Waksman and his colleagues discovered several actinomycetes derived antibiotics.

Because of the widespread use of penicillin, many disease producing organisms had developed a resistance to penicillin (Staphylococci were the first important pathogen that developed resistance to penicillin in 1946). A new step in progress was done in 1960 when first semisynthetic antibiotics were prepared from the penicillin molecule –methicillin and ampicillin which are active against Staphylococci and Gram-negative bacteria.

Definition

Antibiotics are natural metabolic products of fungi, actinomycetes and bacteria that kill or inhibit the growth of microorganisms. Antibiotic production is particularly associated with soil microorganisms and in the natural environment is thought to provide a selective advantage for organisms in their competition for space and nutrients.

Mechanisms of action

One of the ways for classifying antimicrobial agents is on the basis of their site of action (Figure -1). There are many target sites for antimicrobial action:

- 1-Inhibition of cell wall synthesis.
- 2-Inhibition of protein synthesis.
- 3- Inhibition of cell membrane function.
- 4-Inhibition of nucleic acid synthesis.
- 5-Inhibition synthesis of essential metabolites.

These targets differ to a greater or lesser degree from those in the host (human) cells and so allow inhibition of the bacterial cell without concomitant inhibition of the equivalent mammalian cell targets (selective toxicity).

1-Inhibition of cell wall synthesis.

Bacteria have a rigid outer layer, the cell wall. The cell wall maintains the shape and size of the microorganisms which has a high internal osmotic pressure. Injury to cell wall (eg, by lysozyme) or inhibition of its formation may lead to lysis of the cell. The cell wall of most bacteria contains a chemically distinct complex polymer "mucopeptide" "peptidoglycan". Active cells must constantly synthesize new peptidoglycan and transport it to its proper place in the cell envelope. Drugs such as penicillins and cephalosporins (β -lactam) react with one or more of the enzymes required to complete this process, causing the cell to develop weak points at growth sites and to become somatically fragile. Antibiotics that produce this effect are considered bactericidal, because the weakened cell is subjected to lysis. Most of these antibiotics are active only in young, growing cells, because old, inactive, or dormant cells do not synthesize peptidoglycan.

Individual strands of peptidoglycan are composed of alternating amino sugars N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM). These strands are linked together by an enzyme called transpeptidase. This enzyme acts by cleaving the bond between the two terminal D-alanine residues on the NAM unit of the short peptidoglycan chains, then linking the individual chains of peptidoglycan together via β 1-4 linkages to form a rigid structure for support. The peptidoglycan layer is much thicker in the cell wall of Gram-positive than of Gram-negative bacteria.

Synthesis of peptidoglycan precursors starts in the cytoplasm, subunits then transported across the cytoplasmic membrane and finally inserted into the growing peptidoglycan molecules. The important antibiotics groups that act on the cell wall are the β -lactams, glycopeptides, bacitracin and cycloserine.

The initial step in drug action consists of binding of the drug to cell receptors (penicillin-binding proteins; PBPs). These are carboxypeptidase and transpeptidase responsible for the final stages of cross-linking of the bacterial cell wall structure. Different receptors have different affinities for a drug, and each may mediate a different effect. For example, attachment of penicillin to one PBP may result in abnormal elongation of the cell, whereas attachment to another PBP may lead to a defect in the periphery of the cell wall, with resulting cell lysis. PBPs are under chromosomal control, and mutations may alter their number or their affinity for β -lactam drugs.

After a β -lactam drug has attached to one or more receptors, these can not catalyze the transpeptidation reaction, but cell wall synthesis continues. As a result, the newly synthesized cell wall is no longer cross-linked and can not maintain its strength. In addition, the antibiotic-PBP complex stimulates the release of autolysins enzymes that digest the cell wall. The result is a weakened, self-degrading cell wall. Eventually the osmotic pressure differences between the inside and outside of the cell cause lysis. The inhibition of the transpeptidation enzymes by penicillins and cephalosporins may be due to a structural similarity of these drugs to acyl-D-alanyl-D-alanine.