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المضادات الحيوية (BCH 476)

Antibiotics

Lecture 21-22 Mechanism of action of antibiotics

Inhibition of nucleic acid synthesis

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Antimicrobial action through inhibition of Nucleic acid synthesis

(Example 1 Rifampin)

Action on bacteria:

Rifampin inhibits bacterial growth by binding strongly to the DNA-dependent RNA polymerase of bacteria.

Thus, it inhibits bacterial RNA synthesis.

Rifampin resistance results from a change in RNA polymerase due to chromosomal mutations that occurs with high frequency.

Action on viruses:

The mechanism of rifampin action on viruses is different.

It blocks at late stage of assembly of poxviruses.

Antimicrobial action through inhibition of Nucleic acid synthesis

(Example 2 Quinolones)

All quinolones and fluoroquinolones inhibit microbial DNA synthesis by blocking DNA gyrase.

For many microorganisms, p-aminobenzoic acid (PABA) is an essential metabolite.

The specific mode of action of PABA involves condensation of a pteridine with PABA to yield dihydropteroic acid (an adenosine triphosphate (ATP)-dependent reaction), which is subsequently converted to folic acid (an important precursor to the synthesis of nucleic acids).

Antimicrobial action through inhibition of Nucleic acid synthesis

(Example 3 Sulfonamide)

- Sulfonamides are structural analogs of PABA and inhibit dihydropteroate synthetase.
- Sulfonamide can enter the reaction instead of PABA and compete for the active center of the enzyme.
- As a result, nonfunctional analogs of folic acid are formed, preventing further growth of the bacterial cell.
- The inhibiting action of sulfonamides on bacterial growth can be counteracted by excess of PABA in the environment (competitive inhibition).
- Animal cells can not synthesize folic acid and must depend upon exogenous sources.

•Many other bacteria, however, synthesize folic acid as mentioned above and consequently are susceptible to action by sulfonamides.

•**Trimethoprim** (3,4,5-trimethoxybenzyprimidine) inhibits dihydrofolic acid reductase 50,000 times more efficiently in bacteria than in mammalian cells.

•The inhibition of this enzyme prevent the reduction of dihydrofolic acid to tetrahydrofolic acid, which is important in the synthesis of purines and ultimately of DNA.

Sulfonamides and trimethoprim each can be used alone to inhibit bacterial growth.

If used together, they produce sequential blocking, resulting in a marked enhancement (synergism) of activity.

Such mixtures of sulfonamide plus trimethoprim (5:1) have been used in the treatment of *Pneumocystis pneumonia*, malaria, shigella enteritis, systemic salmonella infection, urinary tract infections, and many others.

Pyrimethamine also inhibit dihydrofolate reductase, but it is **more active against the enzyme in mammalian cells** and therefore is more toxic than trimethoprim.

Pyrimethamine plus sulfonamide or clindamycin is the current treatment of choice in toxoplasmosis and some other protozoal infections

Resistance to antimicrobial drugs

There are many different mechanisms by which microorganism might exhibit resistance to drugs .

1- Microorganisms produce enzyme that destroy the active drug.

Example: Staphylococci resistance to penicillin G produce a B-lactamase that destroy the drug.

Other B-lactamase are produced by gram negative rods.

Gram-negative bacteria resistance to aminglycosides (by virtue of a plasmid) produce adenylating, phosphorylating, or acetylating enzymes that destroy the drug.

Gram-negative bacteria may be resistance to chloramphenicol if they produce a chloramphenicol acetyltransferase.

2- Microorganisms change their permeability to the drug. Example: tetracyclines accumulate inside susceptible bacteria but does not enter to the resistance bacteria.

Resistance to polymyxins is also associated with a change in permeability to the drugs.

Streptococci have a natural permeability barrier to aminoglycosides. This can be partly overcome by the simultaneous presence of a cell wall-active drug, e.g. a penicillin.

Resistance to amikacin and to some other amino-glycosides may depend on a lack of permeability to the drugs, apparently due to an outer membrane change that impairs active transport into the cell.

3- Microorganisms develop an altered structural target for the drug.

Example: chromosomal resistance to aminoglycosides is associated with the loss or alteration of a specific protein in the 30S subunit of the bacterial ribosome that severs as a binding site in susceptible organism.

Erythromycin –resistant organisms have an altered receptor on the 50S subunit of the ribosome, resulting from methylation of a 23S ribosomal RNA.

Resistance may be a function of the loss or alteration of PBPs.

Penicillin resistance in *Streptococcus pneumonias* and enterococci is due to altered PBPs.

4- Microorganisms develop an altered metabolic pathway that bypasses the reaction inhibited by the drug.

Example: some sulfonamide–resistant bacteria do not require extracellular PABA but, like mammalian cells, can utilize preformed folic acid.

5- Microorganisms develop an altered enzyme that can still perform its metabolic function but is much less affected by the drug.

Example: in trimethoprim resistant bacteria, the dihydrofolic acid reductase is inhibited far less efficiently than in trimethoprim susceptible bacteria .