NAME-AFABOR MARIAN OGHENERUME

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DEPARTMENT- PHARMACOLOGY

ASSIGNMENT TITLE- ANTIMICROBIAL RESISTANCE

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QUESTION-List and Explain 4 Mechanism of Antimicrobial Resistance.

(1) Enzymatic degradation of antibacterial drugs

(2) Alteration of bacterial proteins that are antimicrobial targets

(3) Changes in membrane permeability to antibiotics. (4) Drug penetration pathway

The four fundamental mechanisms of antimicrobial resistance are (1) enzymatic degradation of antibacterial drugs, (2) alteration of bacterial proteins that are antimicrobial targets, (3) changes in membrane permeability to antibiotics and (4) drug penetration pathway

MECHANISMS OF RESISTANCE DRUG DEGRADATION OR INHIBITION

One mechanism by which bacteria have gained resistance against certain kinds of antibiotics is through the secretion of enzymes that degrade and inhibit the drugs' bacteriostatic and bactericidal properties. Antibiotic resistance coevolved with biosynthesis as a means of bacterial self-immunity strategies for the production of toxic secondary metabolites in antibiotic-producing bacteria. This coevolution strategy could have independently evolved de novo in nonproducing organisms or could be imported via horizontal gene transfer. The genes for resistance, stably integrated into the genome under selective pressure, reflect prior exposure during the evolution of the species.

1-**Enzymatic degradation of antibacterial drugs-**Enzymatic degradation of antibacterial drugs is, perhaps, the major mechanism of bacterial resistance to antimicrobial agents of natural origin. Bacteria have been using this mechanism to resist β-lactam antibiotics by using penicillinases, cephalosporinases, and metallo-β-lactamases. Bacteria have also inhibited aminoglycosides through N-acylases, O-nucleotidylases, O-phosphorylases, adenylases, and aminocyclitol. Bacteria even degrade chloramphenicol and fusidic acid by way of chloramphenicol acetyltransferase.

A common example of this mechanism of resistance formation is the hydrolytic deactivation of the β-lactam ring in penicillins and cephalosporins by the bacterial enzyme β-lactamase. The inactivated penicilloic acid is then ineffective in binding to penicillin-binding proteins (PBPs), thereby protecting the process of cell-wall synthesis. This strategy has also been observed in Enterobacteriaceae against chloramphenicol in a process called acetylation and in Gram-negative and Gram-positive bacteria against aminoglycosides through phosphorylation, adenylation, and acetylation.

2- **ALTERATION OF BACTERIAL PROTEINS**

Bacterial proteins are common targets of antimicrobials. The alteration of bacterial proteins has become a widely used drug resistance mechanism for bacteria. This is one of the three major mechanisms of resistance, along with reduction of drug permeability to its target and drug modification.

Resistance by the general mechanism of drug target modification can be brought about by a remarkable variety of means, which have been exploited by different clinically important bacteria. The modification mechanism often results in an alteration of the original drug target structure, so that the drug binds poorly or not at all. This change in the structure can be brought about by naturally occurring spontaneous mutations in the gene or genes encoding the drug target. These mutations result in modification of single or limited sequences of amino acids in the target protein, often in the region of a known putative drug binding site.

Examples of this mechanism include quinolone resistance due to alterations in target enzymes DNA gyrase and topoisomerase IV involved in DNA synthesis, rifampicin resistance due to alterations in the β-subunit of the target RNA polymerase involved in RNA synthesis, and low-level penicillin resistance in Streptococcus pneumonia due to alterations in the transpetidases (PBPs) involved in cell-wall synthesis.

More extensive modifications of drug targets often require other genetic mechanisms. In the case of high-level penicillin resistance of S pneumonia, more extensive modifications of the target trans peptidases involved in cell-wall synthesis are possible because of this organism's ability to exchange DNA segments with related bacterial species, some of which have trans peptidases that bind penicillin poorly, allowing the generation of mosaic trans peptidases with extensively modified regions of these target enzymes in S pneumonia.

In other cases, such as glycopeptide resistance in enterococci and macrolide resistance in many bacteria, the target structures to which these drugs bind, specifically the cell wall in glycopeptides and the bacterial ribosome in macrolides, are exogenously modified by enzymes encoded by DNA acquired on mobile genetic elements, such as plasmids and transposons, which can be transferred between bacteria. In other cases, such as tetracycline resistance in many bacteria and plasmid-encoded quinolone resistance due to Qnr proteins in enteric Gram-negative bacteria, the drug targets are protected from drug action but not modified by the resistance-determining proteins.

3. ALTERED METABOLIC PATHWAY

Another novel variation of the altered-target mechanism is overexpression of unmodified drug target binding sites in such a way that binding of drug to these extra sites limits access of the drug to a subset of critical target binding sites. This is thought to be the cause of low-level glycopeptide resistance in staphylococci.

Finally, in a number of cases, such as resistance to methicillin and other β-lactams in staphylococci, resistance to mupirocin in staphylococci, and resistance to trimethoprim in many species, bacteria have acquired genes. Sometimes on mobile genetic elements, these acquired genes encode an alternative or bypass drug-resistant target enzyme. This enzyme then provides the functions that would otherwise have been inhibited by the drug, allowing growth in the presence of the antimicrobial.

Some resistant bacteria evade antimicrobials by reprogramming or camouflaging critical target sites to avoid recognition. Therefore, regardless of the presence of an intact and active antimicrobial compound, no binding or inhibition takes place. This type of evasion has been observed in staphylococci against methicillin and other β-lactams, specifically through changes or acquisition of different PBPs that do not sufficiently bind β-lactams to inhibit cell-wall synthesis. Enterococci are able to resist vancomycin by the alteration in cell-wall precursor components to decrease binding of vancomycin. Mycobacterium spp. effectively use this type of mechanism for resistance against streptomycin through modification of ribosomal proteins or rRNA, against the rifamycins through mutations in RNA polymerase, and against the quinolones through mutations in DNA gyrase. Thus, the creativity of nature in developing resistance mechanisms under selective pressure has been capable of meeting the many challenges posed by the development of new antimicrobial drugs.

4. DRUG PENETRATION PATHWAYS

Most antibiotics target intracellular processes, and activity is achieved by penetration of the molecule into the bacteria. The outer membrane of Gram-negative bacteria provides a naturally occurring shield that becomes an additional barrier to molecular penetration of antibiotics.

For these bacterial entities, there are essentially two pathways that allow penetration through the outer membrane. The first mechanism is a lipid-mediated pathway for antibiotics with hydrophobic molecules; the second is via porins that allow general diffusion of hydrophilic antibiotics. Bacterial sensitivity to molecules then becomes a factor of particular lipid and protein compositions of the outer membrane. Drug resistance involving modifications of these lipid and protein macromolecules is common.

In this dual capacity, the outer membrane emerges as a sophisticated macromolecular assembly, the complexity of which has been unraveled only in recent years. By combining a highly hydrophobic lipid bilayer with pore-forming proteins with specific size-exclusion properties, the outer membrane acts as a very selective barrier. The permeability properties of this barrier have a major impact on the susceptibility of the microorganism to antibiotics, which are essentially targeting intracellular processes. Small hydrophilic drugs, such as β-lactams, use the pore-forming porins to gain access to the cell interior, while macrolides and other hydrophobic drugs diffuse across the lipid bilayer. The existence of drug-resistant strains in a large number of bacterial species due to subtle lipid or protein modifications in the composition of the outer membrane highlights the importance of the outer membrane barrier in antibiotic sensitivity.

Porins provide a pathway through the outer membrane for hydrophilic antibiotics, such as β-lactams, as well as tetracycline, chloramphenicol, and fluoroquinolones. Any decrease in the ability or rate of entry of these compounds can lead to resistance. There is an abundance of reports of antibiotic resistance acquired through loss or functional change of porins in a large number of organisms, such as Escherichia coli, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Enterobacter aero genes, and Klebsiella pneumonia.