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Mechanisms of Bacterial Antibiotics Resistance: A Review

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

From the history of human population, it can be concluded that the infections has been one of the major cause of disease. It was thought that this hazard should be resolve with the help of antibiotics. However, bacteria have been able to evolved and become resistant to antibiotics. The increase in antibiotic resistance has been attributed to a combination of microbial characteristics, the selective pressure of antibiotic use and social and technical changes that enhance the transmission of resistant organisms. The growing threat from resistant organisms calls for concerted action to prevent the emergence of new resistant strains and the spread of existing ones. The emerging resistance in today's world has created a major public health dilemma. The major driving force behind the emergence and spread of antibiotic-resistant pathogens is the rapid rise of antibiotic consumption. This trend reflects the growing medicalization of societies worldwide, with its identification of microbial pathogens as the cause of infectious diseases.

Keywords: Resistance; infection; antibiotics; bacteria.

1. INTRODUCTION

Microorganisms are essential component of the biosphere and serve an important role in the maintenance and sustainability of ecosystems. It is believed that they compose about 50% of the living biomass. In order to survive, they have evolved mechanisms that enable them to

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respond to selective pressure exerted by various environments and competitive challenges [1]. The increase in antibiotic resistance has been attributed to a combination of microbial characteristics, the selective pressure of antibiotic use and social and technical changes that enhance the transmission of resistant organisms. The growing threat from resistant organisms calls for concerted action to prevent the emergence of new resistant strains and the spread of existing ones [2]. Currently, antimicrobial resistance among bacteria, viruses, parasites, and other disease-causing organisms is a serious threat to infectious disease management globally [3]. Many procedures use and misuse of antibiotics in man have resulted in antibiotic-resistant bacteria. Although antimicrobial resistance is a natural biological phenomenon, it often enhanced as a consequence of infectious agents' adaptation to exposure to antimicrobials used in humans or agriculture and the widespread use of disinfectants at the farm and the household levels [4]. It is now accepted that antimicrobial use is the single most important factor responsible for increased antimicrobial resistance [5]. Reports of methicillin-resistant *Staphylococcus aureus* (MRSA) a potentially dangerous type of *Staphyloccocci* bacteria that is resistant to certain antibiotics and may cause skin and other infections in persons with no links to healthcare systems have been observed with increasing frequency in the United States and elsewhere around the globe [6]. In Nigeria resistance through *Salmonella typhimurium* has also been reported. Resistance in *Enterococus faecalis* likewise reported [7]. Several reports have been seen also on *Pseudomonas aeruginosa*. This is a bacterial with clearly more resilient and dangerous pathogens which has established themselves in hospitals as stated by [8]. Use of antimicrobials in clinical medicine has exposed the human microbiota to unprecedented high concentrations of these drugs. In-vivo development of de-novo resistance within a human individual has been recorded during treatment courses with a range of antimicrobials [9]. The aim of the article is to review the mechanisms of bacterial antibiotic resistance.

2. MODES OF ANTIBIOTIC ACTION

Different antimicrobial agents act in different ways. The understanding of these mechanisms as well as the chemical nature of the antimicrobial agents is crucial in the understanding of the ways how resistance against them develops. However, the mechanism of action of antimicrobial agents can be categorized further based on the structure of the bacteria or the function that is affected by the agents [10]. These include generally the following:

- Inhibition of the cell wall synthesis.
- Inhibition of ribosome function.
- Inhibition of nucleic acid synthesis.
- Inhibition of foliate metabolism.
- Inhibition of cell membrane function [3].

3. BIOCHEMISTRY OF ANTIBIOTIC RESISTANCE

Several factors have been reported to be responsible to antibiotics resistance in bacterial. Some of the reasons includes: Reduced access to target due to slow porin channels; increased antibiotics expulsion due to multiple drug efflux pumps; inactivating enzymes due to β - lactamases, aminoglycoside-modifying enzymes; mutational resistance due to regulatory mutations that increases the expression of intrinsic genes and operons which is variable in certain circumstances [11]. Although the manner of acquisition of resistance may vary among bacterial species, resistance is created by only a few mechanisms:

1. Antibiotic inactivation – direct inactivation of the active antibiotic molecule [12].
2. Target modification – alteration of the sensitivity to the antibiotic by modification of the target [13].
3. Efflux pumps and outer membrane (OM) permeability changes – reduction of the concentration of drug without modification of the compound itself [14].
4. Target bypass – some bacteria become refractory to specific antibiotics by bypassing the inactivation of a given enzyme [14].

3.1 Antibiotic Inactivation

Bacteria have evolved several mechanisms of rendering antimicrobials inactive such as the enzymatic hydrolysis of antibiotics, group transfer and the redox process [15]. The classical example of this mechanism is the production of β- lactamases that hydrolyze the β-lactam ring of penicillins. These enzymes can often be excreted by the bacteria, inactivating antibiotics before

they reach their target within the bacteria. The classical hydrolytic amidases are the b-lactamases that cleave the b-lactam ring of the penicillin and cephalosporin antibiotics. Many Gram-negative and Gram-positive bacteria produce such enzymes, and more than 200 different b-lactamases have been identified [16]. The second mechanism of antibiotic inactivation involves enzyme mediated structural alteration of the drug *via* transfer of a functional group such as an acyl, ribosyl, phosphoryl or thiol group [15]. The reaction is irreversible and the modified antibiotic is unable to bind to the target due to the resultant change in the structure. The antibiotics susceptible to this bacterial mechanism include aminoglycosides, fosfomycin, macrolides, lincomycin and chloramphenicol [17]. For instance, bacteria have evolved acetyl transferases which inactivate chloramphenicol, tetracycline-metabolizing enzymes that are largely uncharacterized and beta-lactamases that inactivate betalactams such as penicillin [18].

Another form of Antibiotic inactivation is by redox reaction. The oxidation or reduction of antibiotics has been infrequently exploited by pathogenic bacteria. However, there are a few of examples of this strategy [19]. One is the oxidation of tetracycline antibiotics by the TetX enzyme. *Streptomyces virginiae*, producer of the type A streptogramin antibiotic virginiamycin M1, protects itself from its own antibiotic by reducing a critical ketone group to an alcohol at position 16 [11].

3.2 Target Modification

The second major resistance mechanism is the modification of the antibiotic target site so that the antibiotic is unable to bind properly. Because of the vital cellular functions of the target sites, organisms cannot evade antimicrobial action by dispensing with them entirel [19]. In this way, bacteria found ways to alter the molecular targets of antimicrobial agents. Altered targets may include, for example, DNA gyrase, a target of quinolone antimicrobials [20], RNA polymerase, a target of rifampin [21], the prokaryotic ribosome, a target of tetracycline and other protein synthesis inhibitors [22], and targets of antimetabolite drugs, such as the sulfonamides and related drugs [23]. One classical example of drug target modification is the staphylococcal mechanism of variously altering the penicillin binding protein (PBP) which is the target of β-lactam antibiotics [24].

3.3 Efflux Pumps and Outer Membrane (OM) Permeability Changes

One of the most common drug resistance mechanisms is active efflux of drugs from the inside of bacterial cells. In this case, there is reduction of the concentration of drug without modification of the compound itself [14]. The efflux pumps are the membrane proteins that export the antibiotics out of the cell and keep its intracellular concentrations at low levels. Reduced outer membrane (OM) permeability results in reduced antibiotic uptake. The reduced uptake and active efflux induce low level resistance in many clinically important bacteria [25]. Such drug resistant bacteria harbor energy-driven drug efflux pumps which extrude antimicrobial agents thus reducing their intracellular concentrations to sub- or non-inhibitory levels. There are two main types of active efflux pumps. The first type, called primary active transport, uses the hydrolysis of ATP to actively efflux drugs from cells, while the second type, called secondary active transport, uses an ion gradient for active drug efflux from cells [26]. According to Zidic et al. [27] Inducible multidrug efflux pumps are responsible for the intrinsic antibiotic resistance of many organisms, and mutation of the regulatory elements that control the production of efflux pumps can lead to an increase in antibiotic resistance. For example, the MexAB-OprM efflux pump in *Pseudomonas aeruginosa* is normally positively regulated by the presence of drugs, but mutations in its regulator (*mexR*) lead to the overexpression of MexAB-OprM, which confers increased resistance to antibiotics such as b-lactams [28]. Both Gram-positive and Gram-negative bacteria can possess single-drug and/or multiple drug efflux pumps [29].

3.4 Target Bypass

Some bacteria become refractory to specific antibiotics by bypassing the inactivation of a given enzyme [14]. During the process of target bypass, the bacteria alter the molecular targets of antimicrobial agents. Altered targets may include, for example, DNA gyrase, a target of quinolone antimicrobials [30], RNA polymerase, a target of rifampin [31], the prokaryotic ribosome, a target of tetracycline and other protein synthesis inhibitors, and targets of

antimetabolite drugs, such as the sulfonamides and related drugs [32].

4. GENETICS OF ANTIBIOTIC RESISTANCE

Recent metagenomics and functional genomics studies have provided a compelling evidence that antibiotic resistance genes are widespread and the natural reservoirs of potential antibiotic resistance include many ecosystems such as in agriculture [33]. Studies of a wide variety of bacterial pathogens have identified numerous genetic loci associated with antibiotic resistance. For some types of resistance there is a large diversity of responsible genetic determinants. Resistance can be an intrinsic property of the bacteria themselves or it can be acquired. Pehrsson et al. [34] provided an insightful review for the novel resistance functions uncovered using the functional metagenomic examination of various resistance reservoirs. Acquired bacterial antibiotic resistance can result from a mutation of cellular genes, the acquisition of foreign resistance genes or a combination of these two mechanisms. Thus, there are two main ways of acquiring antibiotic resistance; through mutation in different chromosomal loci and through horizontal gene transfer (*i.e.* acquisition of resistance genes from other microorganisms) [34].

A mutation is any heritable change in DNA sequence. Mutation can be beneficial or it can be detrimental. Mutations can be classified by the kinds of alterations in the DNA, or by whether the mutation was spontaneous, or induced by a mutagen in the environment. Mispairing is probably mostly due to cellular processes such as Tautomeric shift of bases, oxidative damage to DNA, Depurination and Deamination or caused by “environment”, i.e, chemicals, radiation, viruses, diet and lifestyle (Mutagens) [35].

5. CONCLUSION

Widespread use of antibiotics has undoubtedly caused the epidemics of antimicrobial resistance worldwide. The development of antimicrobial resistance by bacteria is inevitable and is considered as a major problem in the treatment of bacterial infections in the hospital and in the community. The misuse of antibiotics, interms of application and dosage is an additional contributing factor for the development of antibiotic resistance. The genetic characterization of antimicrobial resistance genes as well as their location and diversity is another important factor for microbial resistance.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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