Research Progress of Antibiotic Resistance

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Abstract. Bacterial resistance which was caused by the abuse of antibiotics is a public health concern in global wide. This article focus on antibacterial mechanism, Bacterial resistance, mechanism antibiotic resistance, and how to retard antibiotic resistance.

1. Introduction

Antibiotics are a serial of chemicals material that can inhibit the growth of bacteria or kill bacteria. Most of them are synthesized by microorganisms in modern time. Antibiotics play an important role in prevention and treatment of various infectious diseases clinically. Abuse of antibiotics has led to antibiotic-resistant in bacteria, which has become an important global concern in public health area\textsuperscript{[1].}

Bacterial resistance was divided into environment-mediated resistance and microbial-mediated resistance; the latter can be divided into intrinsic resistance and acquiring resistance. Generally speaking, resistance which was acquiring with normal genetic background and physiological conditions is inner drug resistant; resistance which was the result from changing in genetic background and changing in cellular physiological conditions is named acquiring resistance. Bacterial resistance is a defensive adaptation to unfavorable environment in bacteria. The specific mechanism of bacterial resistance to antibiotics (including enzyme modification and inactivation of antibiotics, as well as mutation in DNA or over-expression which regulated the target site of antibiotics) and non-specific mechanisms of resistance (including changes in membrane permeability, enhanced membrane efflux of antibiotics and biofilm formation).

Based on the mode of bacteriostasis, antibiotics can be divided into three categories: the first group blocks the synthesis of bacterial cell walls by preventing glycopeptide cross-linking, which lead to no cell wall protection in bacteria, and the consequence is the death of bacteria which due to the changing of osmotic pressure and autolysis’ activity (eg Penicillin) ; the second group works on the bacterial cell membrane phospholipids (such as colistin), or leads to the synthesis of abnormal proteins or bacterial cell membrane permeability increased (such as aminoglycosides); the third group of antibiotics works on blocking the synthesis of bacterial DNA Quinolones), RNA (such as rifampicina), proteins (such as lincomycin) and bacteriostatic or bactericidal\textsuperscript{[2]}. 
2. The Mechanism of Antibiotic Resistance

Bacteria has a continuing mutations during DNA replication cycle. Any altering or displacing intracellular molecules that will cause a serial changing in antibiotics, so that eliminating the target site will lead to the changing in antibiotics resistance. a metabolic antagonist that works on target sites in bacteria will be design and carried out in bacteria life mechanism, and then bacteria resistance will be changed at last. Gene mutations was selected by nature to reduced antibiotic resistance and generate the antibiotic resistant offspring\(^3\). Some people believed that antibiotic resistance genes and synthetic genes have already existing before the use of antibiotics\(^4\). Nature selection works on it too. Moreover, the resistance gene can be transmitted in the form of the plasmid between bacterials\(^5\). It has been found that some bacteria may have multiple drug resistance mechanisms to the same antibiotic, for example, staphylococcal tetracycline resistance system have a change in the target site of and keep active to drug efflux.

Some bacteria can generated enzyme which can be degraded antibiotic or modified antibiotic in chemical structure, which caused the drug inactivation or passivation in antibiotic. Some drug-resistant bacteria, which works on antibiotics with the way of N-acetyltransferase (AAC), O-phosphotransferase (APH) and O-nucleotide transferase (ANT), free hydroxyl phosphorylation and nucleoside, all of these ways reduced the activity of antibiotics\(^6\).

In the early 1990s, Levy proved that bacteria has developed a antibiotics system with the formation of a proactive efflux system\(^7\), and the tetracycline antibiotics mechanism belong to this category. When the Antibiotics come into the bacterial and it begin to activated efflux pump system, the efflux function can be significantly enhanced, and further it works on multi-drug resistance. This process plays an active energy-consuming process, the energy comes from the proton motive force or ATP, and shows energy dependence; the extensiveness of the substrate is another characteristic of the discharge pump system, which is manifested as a variety of Antibiotics, chemical synthetic antibacterials, metalions, disinfectants, detergents, antibacterial dyes and surfactants efflux role. Active efflux pump system is the biological basis of bacterial multi-antibiotic resistance. Active efflux pump systems associated with bacterial multi-antibiotic resistance are mainly five families/classes: ATP-binding cassettes transporters, major facilitator superfamily, Medicine/Metabolite transporter superfamily, Multidrug and toxic compound extrusion family, and Resistance-Nodulation-Division family. The efflux system in different genus is controlled by different genes encoding, for example gonorrhea pneumoniae is a pmrA gene, and staphylococcus aureus is norA gene\(^8\). However, it is still unclear how these efflux systems are activated and regulated.

Changes in target sites for antibiotic action Bacteria can also reduce antibiotics’ work by mutation on the corresponding gene site, with keeping its own normal metabolisms. For example, A transmethylation enzyme, Erm in macrolides which caused adenine of methylates on the 23sRNA transpeptidase; and this process reduced the affinity between antibiotic and bacteria. This process still keep resistant to streptozotocin and streptozotocin\(^9\), the gene mutation mechanism can yielding to multiple antibiotic resistance in bacteria. For example, some mutation of Mycobacterium tuberculosis will lead to antibiotic resistance\(^14\).

Beside this three types of antibiotic mechanism, bacteria still have other way to increase antibiotic ability by changing the bacterial membrane permeability, increasing the product of antibiotic antagonists, changing the metabolic status and so on\(^10\).

Antibiotic resistance testing plays important role in clinical, the traditional method of antibiotic resistance detecting is two-fold dilution in tube and susceptibility testing in disk, these
testing procedures is very nitty and gritty, the test results always affected by a variety of uncertain Factors; and all of these uncertain factor accumulated into a great experimental error at last. With the light of the new advance on genes technology, several new detection methods have been introduced into antibiotic resistance testing area, such as Northern hybridization, Southern hybridization, reverse transcription polymerase chain reaction (RT-PCR), RNase protection assay RNase protection assay and in situ hybridization; immunohistochemistry at the protein level, Western blotting and flow cytometry. There are also single-strand conformation polymorphism and restriction fragment length polymorphism. The development of biochip technology in recent decades has provided a very convenient means for the simultaneous detection of many resistant bacteria\textsuperscript{[11]}.

3. Abuse of antibiotic

Antibiotic resistance is accelerated by human being’s misuse: such as antibiotic abuse and mis-compatible of prescription or over-dose of antibiotics. Abuse of antibiotics is quite normal in feeding poultry, livestock and aquaculture area, Pesticides, herbicides. Antibiotic is widely used to increase agricultural output and purify the environment in large scale. All of these misuse in antibiotic can promote bacterial resistance\textsuperscript{[16]}. In developing country, antibiotic is frequent to prescribe by doctor without any hesitation. Some antibiotic has already spread in nature with the wastewater and pollution. Some identification of antibiotic-resistance gene was found in pristine river urban and agriculture sources\textsuperscript{[18]}. Abuse of antibiotic has already attracted attention of government. More and More restricted law on abuse of antibiotic will be put out on the usage of antibiotic in medical and agricultural area\textsuperscript{[17]}. The usage of antibiotics should be kept under restrictive surveillance and the usage of antibiotics in agricultural field should be carry out reasonably.

4. How to retard the increasing of antibiotic resistance

The research of retarding on antibiotic resistance focus on several area: specific enzyme inhibitors is an effective strategy to overcome enzyme-mediated resistance; the efflux pump system in bacteria works on antibiotic resistance, the development of bacterial efflux pump inhibitors (Efflux pump inhibitors) (such as reserpine) will reduce antibiotic resistance; with the membrane permeability changing, Antibiotics can reach the target site of the bacteria smoothly, this is the membrane permeability mechanism. Some peptide antibacterial works on bacteria in this way\textsuperscript{[12]}. In addition, the structural transformation of antibiotic is another efficient way to overcome resistance in antibiotic. Any change in antibiotic structure will inactive antibiotic-resistant enzymes in bacteria, this is also important way to discover new antibiotics.

Antibiotic susceptibility test is the most rational and effective way in clinic before the use of antibiotics, with the help of drug susceptibility testing, pathogen-infected patients will receive a reasonable etiological examination. Narrow spectrum antibacterial drugs will be selected out according to antibiotic susceptibility test\textsuperscript{[13]}, this will reduce unwanted antibacterials combined application.

The rational use of antibiotics is based on the antibiotic metabolism in body. A reasonable therapeutic regimen will be to determine with antibiotics physical and chemical properties. The first important thing is the schedule of drug intaking; especially for the time-dependent of beta-lactam antibiotics, the specific dosing interval will achieve an effective plasma concentration in body.
Making alternation in using different antibiotics, it makes some bacteria keep from contact with insensitive antibiotics for a period of time, and the resistant bacteria restored to the sensitive bacteria. Such as β-lactam antibiotics can be recycled to maintain its highly effective antibacterial activity and reduce the the production of drug-resistant strains.

Conjugative plasmids is one of important reason to transfer antibiotic resistance among bacteria. Nature and artificial strategies to control the conjugative transmission of plasmid is another option to reduce antibiotic resistance.[15]

5. Summary

The increasing of antibiotics resistance is the result of many factors. With fully understanding the different factors of microbial resistance to antibiotics, the usage of antibiotics will be carry out in reasonable way. Although developing new antibiotics is an effective way to solve the problem of antibiotic resistance, it is not the best and most effective solution. Before clinical use of antibiotics, a drug sensitivity test is better carried out for the pathogen infected with the patients. Only in this way can the doctors examine the current use of antibiotics, choosing appropriate narrow antimicrobial spectrum of antibacterial drugs, while reducing and avoiding unnecessary joint application of antimicrobial agents. The author insists that the most effective drug is selected by drug sensitivity test. China is recently making every effort to regulate and constrain the use of antibiotics. As for the clinical use, a series of regulations and strategies are enacted by the authority to prohibit inappropriate prescription in both public and private hospitals. Another aspect that China lays emphasis on is the need to establish a surveillance system focusing on continuous measurement of antibiotic utilisation and the models of antibiotic resistance. It is believed that surveillance constitutes the very first step of understanding the progression of resistance. Moreover, China has launched its National Action Plan to Contain Antimicrobial Resistance (2016-2020), which aims to strengthen the supervision of antibiotic resistance. All in all, research on the mechanism of microbial resistance need to further on. New drugs should be put into usage with reserved way. The service period of present antibiotics should be extend as far as possible.

References


