UDC 57.047:57.022:57.043:57.044 https://doi.org/10.15407/biotech14.03.022

RESISTANCE TO ANTIBIOTICS AND THEIR UTILIZATION BY MICROORGANISMS

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Received 08.04.2021
Revised 19.05.2021
Accepted 30.06.2021

With the development of antibiotics application, their spread in the natural environment increases dramatically. The presence of antibiotics in the environment changes microorganism and other living beings ratio and composition, which causes a negative impact on biochemical processes that take place in the environment. The spread of antibiotic resistance genes in environmental microorganisms is a growing problem of environmental safety and human health.

Aim. The objectiveof the work was to analyze the adaptation mechanisms of microorganisms to the influence of antibiotics and methods for antibiotics utilization.

Results. The mechanisms of microorganisms' adaptation to antibiotics were shown. The conditions for utilization of different antibiotics classes by microorganisms were provided.

Conclusions. Methods of antibiotics destruction depend on its structure and physicochemical properties. Physicochemical methods were used for local waste purification and were not suitable for antibiotics disposal in the natural environment. The decomposition products could also have a negative effect on the microorganisms' cells.

Depending on the class of antibiotics, their biodegradation occured by different types of microorganisms. It has been shown that sulfonamides and amphinecoles are easily destroyed by many heterotrophic bacteria; biodegradation of aminoglycosides occurs by a strain of *Pseudomonas* spp.; tetracyclines — mushrooms; β-lactams — through the microorganisms' association including *Burkholderiales, Pseudomonadales, Enterobacteriales, Actinomycetales, Rhizobiales, Sphingobacteriales*. A consortium of destructors must be created to dispose the specific classes of antibiotics.

Key words: antibiotics utilization; microorganisms resistance; tetracycline; norfloxancin; resistance factors.

With the development of drugs against infectious diseases, namely antibiotics, they are getting spread in the natural environment with solid waste and wastewater from pharmaceuticals, household, agricultural, etc., which leads to their accumulation in soil, water and sediments [1–3]. Also, antibiotics get introduced into the soil is due to the use of animal manure, bird droppings and sludge from treatment plants as fertilizer [4]. During feeding, antibiotics are only partially metabolized in the liver of animals (30–60% of the administered dose), the rest accumulates in the animal tissues and partially excrements, for example, with manure — up to 20–50% of antibiotics are released unchanged [5]. Soil pollution causes a chain reaction: it affects soil biodiversity, reduces soil organic matter and filtering capacity.

The presence of antibiotics in the environment changes the composition of microorganism associations and other living beings it also changes their ratio, which causes a negative impact on biochemical processes that take place in the environment [6–8]. As a result, the composition of the soil changes, and accordingly its fertility.

Different classes of antibiotics can be also produced by microorganisms that exist in the natural environment. The presence

of such microorganisms in the environment contributes to antibiotics resistance development in the environment due to antibiotic resistance genes (ARG) spread to formerly unresistant microorganisms. Acquisition of such resistance to antibiotics is mainly caused by mobile genetic elements (MGE), such as plasmids, integrons, transposons, transferring resistance from one microorganism to another.

The proliferation of antibiotic resistance genes in environmental microorganisms, especially pathogens, is a problem of great importance for environmental safety and human health [9–11].

The work aims to analyze the mechanisms of microorganisms adaptation to antibiotics influence and methods for their utilization.

Mechanisms of adaptation to antibiotics

Because antibiotics are present in the environment in small quantities, over time, some species of microorganisms adapt to certain classes of antibiotics they were exposed to. The microorganisms resistance to antibiotics is formed due:

– selection of already resistant species using antibiotics (development of new, antibiotic-resistant populations) [12];

– adaptation to the toxic influence of antibiotics caused by cell metabolism changes (metabolic areas affected by the antibiotic are changing to alternative pathways that are not affected by the antibiotic influence, or by the use of already present substrates instead of their synthesis when former requires usage of components that are affected by antibiotics influence);

– production of enzymes that can destroy or damage molecules of the antibiotic [13];

– presence of resistance factors which cause antibiotic transformation into non-toxic form [14];

– change in membrane permeability or increase in active excretion of antibiotics [15, 16].

Also, microorganisms resistant to one type of antibiotic are resistant to other antibiotics with similar structure.

Biochemical mechanisms of microorganism resistance to antibiotics are manifested in the following [17].

Enzymatic inactivation of antibiotics

Inactivation through the enzyme synthesis that specifically interact with the antibiotic and can modify it by following mechanisms:

– destruction of molecular structure and, accordingly, the further impossibility of its interaction with the target molecule;

– molecule inactivation, which leads to a lack of reaction with the target.

Most often, enzymes add an acetyl or phosphate group to antibiotic molecule, which reduces its ability to bind to bacteria ribosome and, consequently, to interrupt protein biosynthesis [18].

Decrease of antibiotic concentration in the cell

Restriction of access to a target molecule is carried out by:

– removal of antibiotic from the microbial cell due to a specialized set of proteins that form transmembrane pumps and are able to transfer toxic substances (except glycopeptides) from the intracellular space to the environment (Figure) [19];

– alteration of the outer membrane permeability due to changes in its composition, which leads to the formation of resistance to several antibiotics groups simultaneously. At the same time it causes a partial loss of pore forming proteins in the membrane [17].

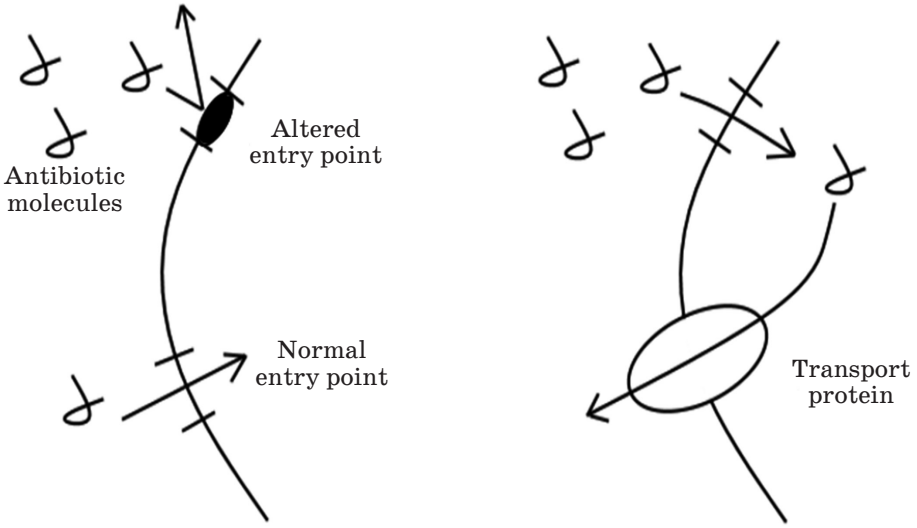
An example is the system of multiple antibiotic resistance (MAR). Thus, on the background of acquired resistance to tetracycline or chloramphenicol, resistance to quinolones and β-lactams is additionally formed. Activation of the MAR system leads to a simultaneous decrease in the amount of one of the pore proteins (OmpF) and increase in one of the excretory systems activity [20].

The cortex of the outer membrane, which consists of liposaccharides, plays a major role in the barrier function of the outer membrane to hydrophobic antibiotics: aminoglycosides (gentamicin and kanamycin), macrolides (erythromycin), rifamycin, novobioclycin, pezoidocin, fuzi and fluoroquinolones. The last two families of antibiotics are also able to penetrate the pores. Bacterial strains that express long oligo- and polysaccharide fragments of lipopolysaccharides have innate resistance to such antibiotics [21].

Modification of the target molecule

The change in the structure of the target molecule may be conducted by the following mechanisms:

– the emergence of spontaneous gene mutations that lead to structural changes in target molecules encoded by them. This



Alteration of entry point to prevent antibiotics from entering cell (Left); transport protein pumping antibiotic molecules out of cell (Right)

disrupts the binding to antibiotic molecule and these mutations stabilize in the presence of antibiotic. As an example, mutations in genes encoding ribosomal proteins RpsL, provide cell resistance to streptomycin; mutations in β-subunits of DNA dependent RNA polymerase — resistance to rifamycin; mutations in DNA gyrase — resistance to quinoline [22];

– the presence of genes transmitted by horizontal transfer. The synthesis products of these genes modify the target molecule, disrupting the antibiotic binding to the target molecule [23];

– acquisition of genes that encode a less sensitive target molecule. For example, the resistance of *Streptococcus pneumoniae* and *Neisseria meningitidis* strains to penicillin is caused by presence of DD-transpeptidase mosaic genes, normal DD-transpeptidase is a target for penicillin [24].

Thus, the resistance of microorganisms to antibiotics is caused by various mechanisms, which are manifested depending on environmental conditions and the class of antibiotic. The spread of antibiotic resistance will lead to economic damage similar to the 2008 financial crisis. It is estimated that due to antibiotic resistance in 2050, world GDP may decline by more than 2–3.5% ($ 100 trillion) [25]. Therefore, it is necessary to provide effective ways of antibiotics disposal to prevent soil and water sources contamination.

Methods of antibiotic disposal

Physico-chemical methods

The sensitivity of bacteria to antibiotics is the main reason for their use, because antibiotics action effectively destroys or stops the development of bacteria. Recently, broad-spectrum antibiotics have been constantly introduced into the animal diet in livestock and poultry for the prevention and treatment of diseases. It has been shown that the administration of antibiotics to livestock and poultry increases the degree of antibiotic resistance in manure and droppings, causing the prevalence of resistance genes [9, 26, 27]. The use of livestock and poultry waste as fertilizer increases the number of resistant microorganisms in the soil, which affects the development of microflora and decrease in soil fertility.

Methods of antibiotic destruction depend on its molecular structure and physicochemical properties.

Existing methods of manure high-temperature treatment that aim to destroy pathogenic microorganisms do no damage to antibiotics molecules. But high temperatures can destroy antibiotic resistance genes (in microorganisms that can survive high temperature) by altering cell metabolism [28].

At pharmaceutical industries with local wastewater treatment commonly used are: oxidation, cavitation and adsorption methods. Ozone, chlorine oxide, chlorine,

sodium hypochlorite, etc. are used in oxidation [8, 26]. As a result, free radicals are formed and the structure of antibiotic molecule is destroyed or is transited to another non-toxic form. It should be noted that decomposition products can also have a negative effect on the microorganisms' cells.

Adsorption processes are used to remove antibiotics using activated carbon, clay and sediment [29]. Adsorption depends on both the physicochemical properties of the sorbent and the properties of antibiotic, namely the molecular structure, functional groups, pH, particle size [6, 30, 31]. Complications that occur during antibiotics sorption by sorbents are associated with the presence of other substances in wastewater, which reduce the disposal efficiency and increases the process cost.

Photodegradation is considered as a promising method of natural antibiotic destruction in the open environment. The destruction process is influenced by such parameters as light source, pH, temperature, time and medium composition [32]. The effect of UV irradiation (100–315 nm, for a period of 60 min) on the destruction of tetracycline and sulfathiazole was studied separately and in a mixture [33]. It is shown that with a separate antibiotics in the solution their complete removal took 14 days for tetracycline and 35 for sulfathiozole. With the mixture of antibiotics, the rate of their destruction was accelerated by 2–4 times depending on the concentration and ratio. This can be explained by the formation of by-products, such as sulfate, which can promote indirect photolysis, and increased hydrolysis by changing the solution pH.

That is, when using photodestruction, a antibiotics mixture or other substances present in the solution can increase the efficiency of destruction. At the same time, the substances formed under the influence of UV radiation can be more toxic than antibiotics.

Biodestruction

Biodegradation of antibiotics occurs by both biotic and abiotic processes. Biotic factor involves the use of microorganisms, and abiotic uses the processes of sorption, hydrolysis, photolysis, oxidation and reduction [34]. Depending on the class of antibiotics, their biodegradation is conducted by different types of microorganisms. 24 genera of bacteria that decompose antibiotics have been identified (*Achromobacter, Acidovorax, Acinetobacter, Alcaligenes, Bacillus, Burkholderia, Castellaniella, Comamonas, Corynebacterium, Cupriavidus, Dechloromonas, Geobacter, Gordonia, Klebsiella, Mycobacterium, Novosphingobium, Pandoraea, Pseudomonas, Rhodococcus, Sphingomonas, Thauera, Treponema, Vibrio* and *Xanthobacter*) [35].

Sulfonylamides are easily destroyed due to division of sulfonamide group by various heterotrophic bacteria isolated from soil and activated sludge [35, 36]. It has been shown that some bacteria (*Achromobacterdenitrificans* PR1, SDZ, SMZ, SPY, *Pseudomonas* sp. DX 7, SMX321, SMX330, SMX331, SMX 333, SMX 336, SMX 342, SMX344, *P. psychrophila* HA-4, *Acinetobacter* sp. HS51, *Rhodococcus rhodochrous* ATCC 13808, *Rhodococcus equi* ATCC 13557, *Alcaligenes faecalis* CGMCC 1.767, *Shewanella oneidensis* MR1, MR4) utilize antibiotics as a source of carbon and energy [35].

It has been established that the removal of sulfodimethoxine (SDZ) and sulfomethaxazole (SMX) by adsorption is almost non-existent. For SDZ removal efficiency after 48 hours in saltwater (SSS) and fresh wastewater (FSS) was 37.3 and 53.4%, respectively. Similar results were obtained for SMX — 22.6 and 39.1% were biodegraded in 48 h in salt and freshwater wastewater, respectively. With the use of the most optimized conditions of wastewater retention in reactors (up to 24 hours) purification from this class of antibiotics due to biodegradation will not be sufficient. The rate of SDZ biodegradation was higher than that of SMX. In addition, the decomposition rate in FSS was higher than in SSS [37].

Trimethoprim is only partially degraded by heterotrophic bacteria from NAS group (*Bacillus subtilis, Pseudomonas aeruginosa, Pseudomonas putida, Rhodococcus equi, Rhodococcus erythropolis, Rhodococcus rhodocrous*, and *Rhodococcus zopfii*) [7].

Aminoglycosides undergo biotransformation [38], but to date only one bacterial strain from the soil was identified (*Pseudomonas* spp.) and some gram-negative bacilli that use streptomycin as a source of carbon and energy. The enzymes involved in this process have not been identified.

Amphenicol antibiotics are destroyed or transformed by various microorganisms [39]. Destruction of the aromatic fragment has been described for only one species (*Pseudomonas* spp. and some gram-negative bacilli), suggesting no further destruction of this part of the molecule.

Tetracyclines. Molecules of this antibiotics class are destroyed mainly by fungi with partial division of four ring stable structure [40].

In a study [29] it was found that concentrations of tetracycline above 2 mg/l leads to inhibition of bacterial growth. It is shown that depending on the initial concentration (50 mg/l–5 mg/l) 44–87% of tetracycline is removed by biodegradation, and 3–6% — by biosorption. It was determined that the spent solid residue contains from 23 mg/kg to 4.5 g/kg of tetracycline, depending on the initial concentration. In addition, one of the biodegradation products of tetracycline was found to be phthalic anhydride, which is more toxic than tetracycline to aquatic organisms. That is, when using the biodegradation of antibiotics, it is necessary to pay attention to the reactions products that may have an inhibitory effect on microorganisms development. It is also necessary to emphasize on the possibility of environmental risks associated with sludge disposal and wastewater emissions.

As shown in [41, 42], tetracyclines are rapidly adsorbed on activated sludge without biodegradation from seawater. The adsorption rate was up to 90% during the first 15 min in FSS and SSS. At the adsorption equilibrium, the removal efficiency in both systems was 98.0 and 92.3%, respectively, in contrast to the adsorption of fluoroquinolones, which differs significantly for these two systems [43].

It has been shown [44] that biodegradation can remove β-lactams by association of microorganisms *Burkholderiales, Pseudomonadales, Enterobacteriales, Actinomycetales, Rhizobiales, Sphingobacteriales*, in contrast to fluoroquinolones and macrolides, for which removal by physicochemical methods is more effective.

It is shown [45–47] that antibiotics undergo biodegradation under changes in conditions (temperature, UV radiation, ozonation, etc.) that are used in wastewater treatment systems. Such changes in conditions allow effective removal of antibiotics, but this approach is not possible in large open systems.

Based on the above, it can be argued that associations of microorganisms used for wastewater treatment, over time, become resistant to certain antibiotics classes used in agriculture, medicine and their production, but are unable to effectively remove them. The presence of antibiotics in the environment reduces the degree of wastewater treatment, biogas yield in case of anaerobic purification, reduces the diversity of microorganisms in associations, resulting in antibiotics entering surface and groundwater, which affects the environment overall [48]. Therefore, to dispose of multiple classes of antibiotics biologically, it is necessary to create strains of bacteria for which antibiotics will serve as a carbon and energy source.

Conclusions

1. The release of antibiotics into the environment affects the diversity of living organisms and all the processes in the environment. In the presence of antibiotics in the medium, some microorganisms species adapt to their influence, which is associated with changes in cell metabolism and the presence of resistance factors, which has a negative impact on environmental safety and human health. This is an incentive to develop effective disposal ways to prevent contamination of soil and water sources.

2. Methods of antibiotics destruction depend on its structure and physicochemical properties. Physico-chemical methods are used for local waste purification and are not suitable for antibiotics disposal in the natural environment. The decomposition products can also have a negative effect on the microorganisms cells.

3. Depending on the class of antibiotics, their biodegradation occurs by different types of microorganisms. It has been shown that sulfonamides and amphinecoles are easily destroyed by many heterotrophic bacteria; biodegradation of aminoglycosides occurs by a strain of Pseudomonas spp.; tetracyclines — mushrooms; β-lactams — through the microorganisms association including: *Burkholderiales, Pseudomonadales, Enterobacteriales, Actinomycetales, Rhizobiales, Sphingobacteriales*. A consortium of destructors must be created to dispose of a specific classes of antibiotics.

The work was done according to the Agreement No 97 BT with Shandong Academy of Sciences, Advanced Material Institute.

The authors declare that they have no conflicts of interest.

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РЕЗИСТЕНТНІСТЬ ДО АНТИБІОТИКІВ ТА ЇХ УТИЛІЗАЦІЯ МІКРООРГАНІЗМАМИ

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З розвитком використання антибіотиків відбувається їх розповсюдження у природному середовищі. Наявність антибіотиків у середовищі змінює склад мікроорганізмів та інших живих істот та їх співвідношення, що спричиннює негативний вплив на біохімічні процеси у довкіллі. Розповсюдження генів стійкості до антибіотиків у мікроорганізмів навколишнього середовища є проблемою екологічної безпеки та здоров'я людини.

Мета. Метою роботи було проаналізувати механізми адаптації мікроорганізмів до дії антибіотиків та методи їх утилізації.

Результати. Наведено механізми адаптації мікроорганізмів до антибіотиків. Показано умови, за яких відбувається утилізація антибіотиків різних класів мікроорганізмами.

Висновки. Методи деструкції антибіотиків залежать від їхньої структури та фізико-хімічних властивостей. Фізико-хімічні методи використовують для локального очищення і не застосовують для утилізації антибіотиків у природному середовищі. При цьому продукти розкладу також можуть справляти негативний вплив на клітини мікроорганізмів.

Залежно від класу антибіотиків їхня біодеструкція відбувається різними видами мікроорганізмів. Показано, що сульфаніламіди і амфінеколи легко руйнуються багатьма гетеротрофними бактеріями; біодеградацію аміноглікозидів спричинює штам *Pseudomonas* spp.; тетрациклінів — грибами; β-лактамів — за допомогою асоціації мікроорганізмів *Burkholderiales, Pseudomonadales, Enterobacteriales, Actinomycetales, Rhizobiales, Sphingobacteriales.* Для утилізації конкретного класу антибіотиків необхідно створювати консорціум деструкторів.

Ключові слова: утилізація антибіотиків; резистентність мікроорганізмів; тетрациклін; норфоксанцин; фактори резистентності.

РЕЗИСТЕНТНОСТЬ К АНТИБИОТИКАМ И ИХ УТИЛИЗАЦИЯ МИКРООРГАНИЗМАМИ

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С развитием использования антибиотиков происходит их распространение в природной среде. Наличие антибиотиков в среде изменяет состав микроорганизмов и других живых существ и их соотношение, что оказывает негативное влияние на биохимические процессы, протекающие в окружающей среде. Распространение генов устойчивости к антибиотикам у микроорганизмов является проблемой экологической безопасности и здоровья человека.

Цель. Целью работы является анализ механизмов адаптации микроорганизмов к действию антибиотиков и методов их утилизации.

Результаты. Приведены механизмы адаптации микроорганизмов к антибиотикам. Показаны условия, при которых происходит утилизация антибиотиков различных классов микроорганизмами.

Выводы. Методы деструкции антибиотиков зависят от их структуры и физико-химических свойств. Физико-химические методы используют для локальной очистки и не применяют для утилизации антибиотиков в естественной среде. При этом продукты разложения также могут оказать негативное влияние на клетки микроорганизмов.

В зависимости от класса антибиотиков их биодеструкция происходит различными видами микроорганизмов. Показано, что сульфаниламиды и амфинеколы легко разрушаются многими гетеротрофными бактериями; биодеградация аминогликозидов происходит штаммом *Pseudomonas* spp.; тетрациклинов — грибами; β-лактамов — с помощью ассоциации микроорганизмов *Burkholderiales, Pseudomonadales, Enterobacteriales, Actinomycetales, Rhizobiales, Sphingobacteriales.* Для утилизации конкретного класса антибиотиков необходимо создавать консорциум деструкторов.

Ключевые слова: утилизация антибиотиков; резистентность микроорганизмов; тетрациклин; норфоксанцин; факторы резистентности.