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Review

Influence of antibiotics on the development of mitochondrial dysfunction

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Abstract

Antibiotics are an indispensable component of therapeutic strategies in the treatment of severe bacterial infections. Unfortunately, in addition to the emerging resistance of bacteria to antibiotics, side effects are an important problem with their use. Knowledge of the mechanisms underlying the development of side effects can make it possible to understand how it is possible to reduce their negative impact on the health of patients. One of the negative effects of antibiotics on the human organism is interference with homeostasis and the functioning of mitochondria. Side effects of antibiotics based on this influence require further study. Here we consider the mitochondria as a side target of antibiotics and the main strategies of antibiotics that cause mitochondrial dysfunction. Options are also considered on how to deal with this problem and even use it for good.

Keywords: Antibiotics; Oxidative stress; Mitochondria; Tetracyclines; Aminoglycosides

1. Introduction

Antibiotics are compounds that target bacteria and are thus designed to treat and prevent bacterial infections. The first antibiotic, salvarsan, was used in 1910. In just 100 years, antibiotics have fundamentally changed modern medicine and increased the average human life expectancy by 23 years [1]. Antibiotics have been the backbone of medicine for many years and have been used worldwide on a massive scale. In many countries, the use of antibiotics exceeds one course per capita per year. In just one year, the seven major classes of antibiotics were consumed in approximately 70 billion individual doses, corresponding to approximately 10 tablets per person [2].

To fully appreciate the importance of antibiotics in daily life, it is necessary to go back to the edge of the pre-antibiotic era when these life-saving drugs were first introduced into clinical use. In the pre-antibiotic era, skin and soft tissue infections such as cellulitis and erysipelas were often fatal. These serious infections of the subcutaneous fascia can affect the lymphatics and spread systemically. In the pre-antibiotic era, bacteremia was common, with mortality as high as 15%. The introduction of sulfonamides into clinical use in the 1930s changed the situation, and as a result, mortality decreased to 2% [3]. Streptococcus pneumoniae pneumoniae was also a fatal disease. Approximately 30% of patients died from this infection. If the patient had bacteremia, mortality was expected in 70-90% of people. Among the survivors, only 30% had no fever for one week. Penicillin therapy reduced mortality from bacteremic pneumonia to 17%. Therapy with sulfonamides resulted in the absence of fever in 70-80% of patients within three days. Before antibiotics, endocarditis was a deadly infection. Today, the overall mortality rate is about 20% for antibiotics and for surgery when indicated. Mortality associated with infectious diseases was declining by the early 20th century, and this decline accelerated (with the exception of the 1918 influenza pandemic) with the introduction of sulfonamides and penicillin in the 1930s and 40s [3].

While antibiotics are valuable in treating severe and potentially fatal infections, they can also lead to increased bacterial resistance and adverse outcomes. All medicines have the potential for adverse reactions, and antibiotics are no exception. One in five hospitalized patients has been

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shown to develop an adverse reaction to an antibiotic, and almost the same proportion of emergency room visits are associated with adverse reactions to antibiotics [4]. An immune-mediated reaction or hypersensitivity is classified as an allergy [5]. This includes IgE-mediated anaphylaxis and angioedema. Drugs often reach harmful levels in the body due to decreased metabolism and excretion, or high dosage regimens can cause toxicity due to exceeding therapeutic drug levels. If a reaction occurs that is not mediated by the immune system and is not related to the level of the drug, then it is considered a side effect [6].

All of the antibiotics evaluated can cause gastrointestinal effects (eg, nausea, vomiting, diarrhea, abdominal pain, anorexia, bloating), often due to disruption of the intestinal flora. Broad-spectrum antibiotics can also cause overgrowth of secondary Candida species, especially in diabetic patients [6].

The expectation of adverse events is justified when starting antimicrobial therapy. Some patients are at higher risk, such as the elderly, patients with multiple comorbidities, and hospitalized patients [4]. It is important to monitor patient reactions as many develop over time. Some antibiotics require drug-level monitoring to determine the effectiveness of therapy and prevent side effects, such as vancomycin and aminoglycosides [7]. Renal toxicity may develop if these antimicrobials maintain high trough levels; therefore, monitoring of renal function is necessary, in addition to measuring drug levels.

Accurate knowledge of the side effects caused by antibiotics is essential for the quality treatment of infectious diseases. Understanding the intracellular mechanisms leading to the development of side effects will allow the development of safer antibiotics in the future.

2. Classes of used antibiotics

2.1. Aminoglycosides

Aminoglycosides are natural or semi-synthetic antibiotics derived from actinomycetes. Aminoglycosides have a broad spectrum of activity covering aerobic organisms, including gram-negative bacteria and mycobacteria. Aminoglycosides are particularly effective against members of the Enterobacteriaceae family, including *Escherichia coli, Klebsiella pneumoniae* and *K. oxytoca*. In addition, aminoglycosides are active against *Yersinia pestis* and *Francisella tularensis*, the causative agents of plague and tularemia, respectively. This class also has good activity against *Staphylococcus aureus*, including methicillin-resistant and vancomycin-intermediate and resistant isolates [8]. Aminoglycosides have bactericidal activity in which they bind to the 30S subunit of the bacterial ribosome. In particular, they are thought to bind to the A site (aminoacyl) on the 16S rRNA, a component of the 30S ribosomal subunit. Due to this binding, the genetic code is misread and translation is disrupted, which leads to the fact that bacteria cannot perform protein synthesis [9].

Because there are several drugs in the aminoglycoside class, including gentamicin, tobramycin, amikacin, neomycin, plasmomycin, paromomycin, and streptomycin, indications vary for different individual aminoglycosides. As a rule, indications for the use of aminoglycosides include both empirical and directed treatment. Because this class of agents has been shown to be effective against multidrug-resistant Gram-negative pathogens, aminoglycosides are indicated for empiric therapy in patients with severe disease; this includes empiric treatment of patients with infective endocarditis, sepsis, complicated intra-abdominal infections, and complicated genitourinary infections [9]. The main reported side effects of aminoglycosides are ototoxicity, nephrotoxicity, and neuromuscular blockade. Aminoglycosides should be avoided in patients with myasthenia gravis due to the risk of prolonged neuromuscular blockade [10,11].

2.2. Beta-lactam antibiotics

Beta-lactams are the most widely used class of antibiotics against infectious diseases [12]. From a biochemical point of view, these preparations have a common feature consisting of 3 carbon atoms and 1 nitrogen atom (beta-lactam ring), which are highly reactive. This class includes penicillins, cephalosporins, carbapenems, monobactams, and beta-lactamase inhibitors [13]. Indications for beta-lactam antibiotics range from small boils, carbuncles, respiratory and urinary tract infections, ear or eye infections, and gonorrhea, to life-threatening conditions such as ventilator-associated pneumonia, meningitis, septicemia, and gangrene, to prophylactic use in bacterial endocarditis, agranulocytosis or other immunosuppressed situations and for the prevention of surgical site infections secondary to proper aseptic and antiseptic measures. Beta-lactam antibiotics inhibit the last step in the synthesis of peptidoglycan (an important component of the bacterial cell wall) by acylating transpeptidase involved in the cross-linking of peptides to form peptidoglycan. The targets of action of beta-lactam antibiotics are known as penicillin-binding proteins (PBPs). This binding, in turn, interrupts the terminal process of transpeptidation and causes loss of viability and lysis, including through autolytic processes inside the bacterial cell [14].

A serious problem associated with beta-lactams is the growing resistance. This applies primarily to Streptococcus pneumoniae and individual Gram-negative rods such as Pseudomonas aeruginosa. The resistance of bacteria to beta-lactams is mainly expressed in the production of beta-lactamases, reduced penetration into the target site, changes in the PBP of the target site and efflux from the periplasmic space through specific pumping mechanisms [14].

Compared to other classes, beta-lactam drugs are generally safe and well tolerated. The most common side effects are allergic reactions, which range from 0.7% to 10%. These reactions can occur with any formulation of penicillin and are mostly a maculopapular rash, while anaphylaxis has been reported in 0.004% to 0.015% of patients. Penicillins are contraindicated in patients with previous anaphylactic reactions or severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrosis [15].

2.3. Macrolides

Macrolides are bacteriostatic antibiotics with a broad spectrum of activity against many Gram-positive bacteria. In particular, azithromycin, clarithromycin, and erythromycin are commonly used to treat infections such as pneumonia, sinusitis, pharyngitis, and tonsillitis. In addition, antibiotic use has been approved for uncomplicated skin infections and otitis media in children. Macrolides are also widely used to treat sexually transmitted infections such as gonococcal and chlamydial infections [16]. There

are currently five macrolide antibiotics available for use: erythromycin, clarithromycin, azithromycin, fidaxomicin, and telithromycin, the latter being the related ketolide. Erythromycin was originally isolated in 1952 from Streptomyces erythreus; the remaining macrolide antibiotics are semi-synthetic derivatives. The five macrolide antibiotics have a similar spectrum of activity, showing bacteriostatic activity against many strains of *Streptococcus, Staphylococcus, Clostridium, Corynebacterium, Listeria, Haemophilus influenzae, Moxicellus* and *Neisseria meningitidis* [17].

The mechanism of action of macrolides is based on their ability to bind the 50S subunit of the bacterial ribosome, causing the cessation of bacterial protein synthesis. Once bound, the drug prevents translation of the mRNA, especially the growing peptide chain, preventing the addition of the next amino acid to the tRNA. Because the bacterial ribosomal structure is highly conserved in most if not all bacterial species, it is thought to have a wide spectrum. Macrolides are considered bacteriostatic because they only inhibit protein synthesis, although at high doses they can be bactericidal [18].

Like any other antibiotic, macrolides carry a significant risk of typical side effects such as nausea, vomiting, abdominal pain, and diarrhea. Abdominal symptoms are largely a result of macrolides being motilin agonists, causing an increased risk of gastrointestinal distress and side effects. In addition, the intestinal flora is sensitive to the action of macrolides; therefore, it may cause an imbalance between commensal bacteria living in the human gut and pathogenic bacteria that need to be controlled [19].

2.4. Tetracyclines

Tetracyclines are a class of broad-spectrum antibiotics used to treat a variety of infectious diseases. Natural drugs in this class are tetracycline, chlortetracycline, oxytetracycline, and demeclocycline. Semi-synthetic tetracyclines include lymecycline, metacycline, minocycline, roletetracycline, and doxycycline. There is also a class of newer tetracyclines that includes ervacycline, sarecycline, and omadacycline [13]. These drugs can treat rickettsial infections, ehrlichiosis, anaplasmosis, leptospirosis, amoebiasis, actinomycosis, nocardiosis, brucellosis, melioidosis, tularemia, chlamydial infections, pelvic inflammatory disease, syphilis, travelers' diarrhea, early Lyme disease, acne, Legionnaires' disease, and Whipple's disease. Prevention of meningococcal infection is also possible [20].

Tetracyclines specifically inhibit the 30S subunit of the ribosome, preventing the binding of aminoacyl -tRNA to the acceptor site of the mRNA-ribosome complex. When this process stops, the cell can no longer maintain normal functioning and cannot grow or reproduce further [20].

Bacterial strains resistant to tetracycline antibiotics are a growing concern. Bacterial tetracycline-resistant genes are often encoded on plasmids or transferable elements such as transposons. Two well-documented resistance mechanisms involve alteration of ribosomal defense proteins or efflux pumps. The first mechanism allows ribosomes to continue protein synthesis regardless of high intracellular drug levels. The latter mechanism consists of various subtypes of transmembrane pumps that expel solutes, in this case, antimicrobials, from the cell to prevent cell death [21].

A disadvantage of tetracyclines is that they can cause gastrointestinal disturbances including abdominal discomfort, epigastric pain, nausea, vomiting, and anorexia. Against the background of taking tetracyclines, it is possible to change the color of the teeth and inhibition of bone growth in children. Some patients experience photosensitivity, which may present with a red rash or blistering of the skin. Less commonly, tetracyclines can cause hepatotoxicity and exacerbate pre-existing renal failure [22].

2.5. Glycopeptide antibiotics

Glycopeptide antibiotics (GPAs) are often used to treat life-threatening infections caused by multidrug-resistant Gram-positive pathogens such as *Staphylococcus aureus*, *Enterococcus spp.* and *Clostridium difficile*. They are the drugs of last resort against methicillin-resistant Staphylococcus aureus (MRSA), which is currently the leading cause of community-acquired infections and leads to high rates of morbidity and mortality in hospital-acquired infections. The common structural motif is a basic heptapeptide scaffold containing aromatic amino acids that have undergone extensive oxidative crosslinking and attachment of various moieties such as sugar residues, chlorine atoms, and lipid chains. Vancomycin and teicoplanin represent the first generation of clinically important GPA [23].

These antibiotics primarily attack the outer membrane of sensitive bacteria. The amino group of the cyclic polypeptide part of the drug forms an electrostatic interaction with the binding site of the divalent lipopolysaccharide cation of the outer membrane of bacteria, destroying the integrity of the outer membrane. Thus, the fatty acid part of the drug can penetrate the outer membrane, thereby increasing the permeability of the cytoplasmic membrane, which leads to the release of small molecules such as phosphoric acid and nucleoside into the cytoplasm, causing direct cell dysfunction. Due to the thick cell wall on the outside of gram-positive bacteria, which prevents the penetration of the drug into bacteria, such antibiotics do not act on them [24].

Side effects of this class of antibiotics include infusion reactions, nausea, diarrhea, taste disturbance, and foamy urine. Telavancin may also cause impaired renal function and prolongation of the QTc interval. Rare side effects include hypersensitivity reactions, renal failure and Clostridium difficile (pseudomembranous) colitis [25]. General data on antibiotic classes are summarized in Table 1.

3. Oxidative phosphorylation in health and disease

Most of the usable energy derived from the breakdown of carbohydrates or fats comes from oxidative phosphorylation occurring in the mitochondria. For example, the breakdown of glucose by glycolysis and the tricarboxylic acid (TCA) cycle yields a total of four ATP molecules, ten NADH molecules, and two FADH2 molecules. Electrons from NADH and FADH2 are then transferred to molecular oxygen, which is associated with the formation of an additional 32–34 ATP molecules by oxidative phosphorylation. Electron transport and oxidative phosphorylation are critical functions of protein complexes in the inner mitochondrial membrane, which ultimately serve as the main source of cellular energy [26].

The process of electron transfer from NADH to protein complexes and, finally, to oxygen is complex. There are four protein complexes involved in electron transport that function as enzymes in the electron transport chain (ETC).

Table 1. Summarized data on antibiotics used in medicine.

Class of antibiotics	Target	Side effects
Aminoglycosides	30S bacterial ribosome	ototoxicity, nephrotoxicity, and neuromuscular blockade
Beta- lactam antibiotics	peptidoglycan	allergic reactions
Macrolides	50S bacterial ribosome	abdominal symptoms
Tetracyclines	30S bacterial ribosome	abdominal symptoms
Glycopeptide antibiotics	Outer bacterial membrane	infusion and abdominal reactions, impaired renal function

These enzymes carry out oxidation and reduction reactions, allowing sequential transfer of electrons from one complex to another. The first complex (complex I) in the ETC is called NADH dehydrogenase because of its role in the oxidation of NADH to NAD+. This complex has an enzymatic activity that allows the transfer of an electron pair from NADH to ubiquinone (Q). An electron pair from NADH is first transferred to NADH dehydrogenase by a flavin mononucleotide (a derivative of riboflavin or vitamin B2), an accompanying prosthetic group. Within the complex, an electron pair is sequentially transferred from one iron-sulfur (Fe-S) cluster to another to eventually reach ubiquinone. Then ubiquinone is reduced to ubiquinol and passes into complex II [27]. Complex II is called succinate dehydrogenase because of its role in the oxidation of succinate to fumarate in the TCA cycle. It is also the electron transfer point for FADH2. This enzyme transfers electrons from FADH2 to the ubiquinone molecule. This relatively small complex contains iron-sulfur clusters and an associated cofactor, flavin adenine dinucleotide (FAD). Electrons from complexes I and II are transferred by ubiquinone (in the form of ubiquinol) to complex III [28]. Complex III is called cytochrome C reductase because of its role in the reduction of cytochrome C. This complex consists of several molecules, including cytochrome B and many iron-sulfur clusters, all of which are involved in electron transfer to cytochrome C. The enzymatic action of complex III includes the transfer of electrons from ubiquinol to cytochrome C and subsequent pumping of 4 H+ ions into the intermembrane space. Although ubiquinol can donate two electrons, cytochrome C can only accept one electron. Complex IV completes the respiratory chain by accepting electrons from cytochrome C to completely reduce oxygen to water [29]. The successive reduction/oxidation (redox) reactions in the ETC cause conformational changes in the respiratory complexes that allow them to pump protons from the matrix into the intermembrane space, creating an electrochemical gradient known as the mitochondrial transmembrane potential (Djm). The proton gradient created by complexes I, III, and IV creates a proton driving force used by (adenosine triphosphate) ATP synthase (complex V), which phosphorylates (adenosine diphosphate) ADP to form ATP [26].

The tight association between proteins in the respiratory complexes can optimize substrate canalization, minimizing electron slippage and hence the formation of reactive oxygen species (ROS). However, electron transport can proceed and react with oxygen to form superoxide, a precursor of ROS. Complex I and complex III are the main sources of its production, although complex II may also contribute to ROS production [30]. ROS in moderate amounts can regulate cellular signaling, including proper cellular differentiation, tissue regeneration, and prevention of aging [26]. However, excess ROS can contribute to metabolic oxidative stress, cell damage, and genomic instability. Once mitochondrial DNA is damaged, it becomes a target for oxidative damage and can increase oxidative stress by reducing the expression of critical proteins that are important for electron transport. This, in turn, creates a vicious circle of ROS production and organelle damage, which ultimately leads to apoptosis [31]. Oxidative damage due to constant exposure to ROS results in damage to mitochondria and cellular lipids, proteins, and nucleic acids. Acute exposure to ROS leads to disruption of the Fe–S centers of complexes I, II, and III of the electron transport chain and aconites of the tricarboxylic acid cycle, which leads to a stop in the production of mitochondrial energy [32].

4. Model of the influence of antibiotics on the development of mitochondrial dysfunction

The target effect of antibiotics is represented by several mechanisms of action on the components of a bacterial cell. Among the main targets of antibiotics located in the bacterial cell, the cell wall, ribosomes and DNA are isolated. Antibiotics act on the cell wall, inhibiting the assembly of the peptidoglycan layer, which leads to the lysis of the bacterial cell [34]. As a result of their action on bacterial ribosomes, antibiotics are able to bind to both subunits of the ribosome: 30S and 50S, which in both cases leads to translation inhibition [35]. When targeting bacterial DNA, antibiotics inhibit the replication process, which prevents the bacterial genetic material from spreading [36]. Despite the high efficiency of antibiotics in the treatment of a number of severe bacterial infections, antibiotics have side effects, the development of which may be associated with non-targeted pathological effects of antibiotics on processes occurring in human tissue cells. Thus, the possibility of inhibition of DNA replication [37] and protein synthesis [38] was shown when antibiotics were introduced into a culture of eukaryotic cells. In addition, data are accumulating on the ability of antibiotics to interact with mitochondria [39]. This mechanism is explained by the endosymbiotic theory, according to which mitochondria originated from intracellular symbiont bacteria, which partly explains the similarity in the structure of bacteria and mitochondria [40]. We identified three pathways for the action of antibiotics on mitochondria: inhibition of mitochondrial protein synthesis, induction of oxidative stress, and changes in cell bioenergetics.

4.1. Inhibition of mitochondrial protein synthesis

In addition to the fact that mitochondria contain their circular genome, they also have bacterial-type ribosomes in animal cells represented by 55-60 S ribosomes [39]. The effect exerted by antibiotics on mitochondrial ribosomes

is similar to their effect on bacterial ribosomes and leads to mitochondrial dysfunction. Thus, antibiotics of the families of aminoglycosides, amphenicols, lincosamides, macrolides, oxazolidinones, and streptogramins, whose mechanism of action is based on the inhibition of bacterial protein synthesis, are similarly able to inhibit the synthesis of mitochondrial proteins by acting on mitochondrial ribosomes, but without affecting the ribosomes located in the cytoplasm [39]. The antibiotic cycloheximide, which is an antifungal compound, on the contrary, does not have a negative effect on mitochondrial ribosomes, but it affects protein synthesis in cytoplasmic ribosomes [41]. This disruption of translation leads to an imbalance between the mitochondrial proteins encoded in the mitochondria and in the nucleus [42]. The resulting imbalance has a negative effect on oxidative phosphorylation, which is reflected in a decrease in the rate of oxygen uptake and a decrease in the overall efficiency of the respiratory chain reactions [43]. In addition, changes in mitochondrial dynamics are noted, leading to an increase in mitochondrial division and a weakening of mitochondrial fusion, which leads to an increase in the number of fragmented and dysfunctional mitochondria in the cell [43]. Mitochondrial dysfunction caused by mitonuclear imbalance leads to activation of the mitochondrial unfolded protein response (UPR mt) [42]. Even though UPR mt is an adaptive response of the body to a stressful state, its long-term activation can also lead to negative consequences, including the spread of mutant mitochondrial genomes, resulting in increased mitochondrial dysfunction, and mitochondrial damage, which is one of the initiating factors of apoptosis [43].

4.2. Oxidative stress induction

The similarity of bacterial cells with mitochondria suggests that the mechanism of action of bactericidal antibiotics, leading to the death of bacteria, can also manifest itself when these antibiotic variants bind to the mitochondria of eukaryotic cells. Thus, it has been shown that the main classes of bactericidal antibiotics, regardless of their final target, cause the induction of oxidative stress as a result of disruptive interference in the processes of the tricarboxylic acid cycle (TCA) and the electron transport chain (ETC), which leads to an increase in the level of reactive oxygen species (ROS) to lethal concentrations that cause the death of bacterial cells [44]. A similar effect was found in the study of the effect of bactericidal antibiotics on various cell cultures of human tissues and in vivo in a mouse model. It has been shown that bactericidal antibiotics from the classes: quinolones (ciprofloxacin), aminoglycosides (kanamycin) and β-lactams (ampicillin) in clinical doses cause oxidative stress in eukaryotic cells, which leads to damage to macromolecules: proteins, lipids and DNA [45],[46],[47]. The resulting oxidative stress is associated with the inhibition of ETC complexes by antibiotics, which leads to electron leakage and promotes an increase in ROS generation. As a result of this inhibitory effect, the activity of complex I decreased by 16-25%, and the activity of complex III decreased by 30-40% compared with untreated samples. The consequences of mitochondrial dysfunction, in addition to oxidative stress, included a decrease in mitochondrial membrane potential, ATP production, and overall metabolic activity. It is known that oxidative stress is one of the factors initiating the internal pathway of apoptosis, which may be the final stage of cellular pathological reactions of bactericidal antibiotics. It should be noted that a similar administration of the bacteriostatic antibiotic tetracycline did not cause oxidative stress and mitochondrial dysfunction [48].

4.3. Impact on bioenergy

The consequences of mitochondrial dysfunction caused by the action of antibiotics also lead to changes in the energy and metabolic state of the cell. First of all, the main metabolic consequence of mitochondrial dysfunction is a decrease in the efficiency of oxidative phosphorylation, which is associated primarily with a decrease in ATP production. In a state of energy stress, cells are forced to rebuild their metabolism in the direction of less efficient, but faster energy production - aerobic glycolysis. This shift in metabolism was first noted for cancer cells and is called the "Warburg effect". In a study [49], it was demonstrated that the antibiotic azithromycin increased the expression of glycolytic enzymes and glucose transporters in mammary gland cells, which consequently led to an increase in aerobic glycolysis, as well as the accumulation of lactate. A similar effect was found when analyzing the effect of gentamicin on human cell culture [50]. The ability of antibiotics to directly affect host metabolism has been shown in a study in a mouse model [51]. As a result of a disruption of oxidative phosphorylation, as well as a marked increase in hypoxia, the efficiency of oxidation of various catabolic substrates decreases. For example, beta-oxidation of fatty acids may decrease [52], [53], [54]. Severe disruption of energy metabolism can lead to the accumulation of harmful metabolites and the development of cell energy dysfunction, which leads to further cell death.

4.4. Health implications of mitochondrial dysfunction

Antibiotic-induced mitochondrial dysfunction can lead to various pathological complications and be a potential cause of a number of diseases. So some of the side effects of aminoglycosides, such as kidney damage, ototoxicity, and vestibular toxicity have been shown to result from mitochondrial dysfunction. A direct link between antibiotic-induced mitochondrial dysfunction and the development of disease has not been proven but is actively discussed. In particular, the immunosuppressive effect of antibiotics has been shown, caused by inhibition of the translation of mitochondrial proteins in T cells, which may be the cause of weakened immunity when taking antibiotics in the treatment of bacterial infections [55]. Also considered is the potential role of antibiotic use in the development of obesity, which can be caused as a result of excessive accumulation of fatty acids in adipocytes due to metabolic disorders due to mitochondrial dysfunction [52]. Antibiotic-induced oxidative stress is also a factor in the pathogenesis of oncological, neurodegenerative, and cardiovascular diseases (such as atherosclerosis), which determines the potential role of antibiotics in initiating these diseases [56].

The general model for the development of antibiotic-induced mitochondrial dysfunction is shown in Figure 1.

5. Discussion

Understanding the processes underlying the occurrence of side effects of antibiotics allows not only to better understand the mechanism of their action but also helps to find effective ways to reduce toxicity. Thus, in the already

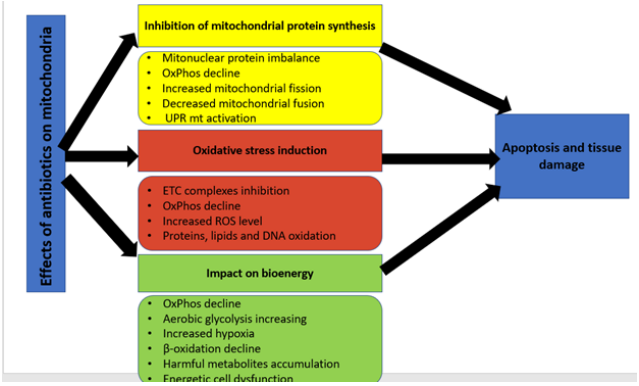

Fig. 1. General model for the development of antibiotic-induced mitochondrial dysfunction.

mentioned early study, the introduction of N-acetyl-L-cysteine, which is an antioxidant, led to a decrease in oxidative stress and the restoration of mitochondrial function in eukaryotic cells [48]. It is important to mention that N-acetyl-L-cysteine did not reduce the effectiveness of bactericidal antibiotics when tested in bacterial cultures and in a mouse model of urinary tract infection. However, in a study on the combined use of glutathione (another antioxidant) with bactericidal antibiotics, a decrease in the effectiveness of the antibiotic in killing bacterial cells was noted [57]. It follows from this that in order to simultaneously maintain efficacy and ensure a reduction in toxicity in combination therapy of antibiotics with antioxidants, additional studies are required testing various antioxidant compounds together with bactericidal antibiotics in various types of bacterial and eukaryotic cell cultures. On the other hand, antibiotic-induced mitochondrial dysfunction may have a beneficial effect on medical applications. Thus, in a study [58] with the introduction of antibiotics azithromycin and doxycycline, combined with a triphenylphosphonium cation for better targeting of mitochondria, the ability of the obtained compounds to reduce the mitochondrial function of cancer cells and reduce their proliferation was shown. In another study [53], the administration of the antibiotic linezolid protected mice from experimental autoimmune encephalomyelitis, as a result of inhibition of the translation of mitochondrial proteins (primarily mEF-G1), which reduced the efficiency of oxidative phosphorylation and the concentration of NAD +, which reduced the production of cytokines by T-helper-17, which are one of the main initiators of the autoimmune reaction.

6. Conclusion

The use of antibiotics is often an indispensable therapeutic strategy in the treatment of a number of infectious diseases. However, serious side effects with some antibiotics make antibiotic therapy less safe. Antibiotics can affect not only bacterial but also eukaryotic cells, which is the reason for the development of toxicity. One of the key targets of antibiotics in eukaryotic cells is the mitochondrion. Antibiotics are able to act on mitochondria through inhibition of mitochondrial protein synthesis, restriction of the activity of the respiratory centers, and a shift in metabolic activity towards glycolysis. Subsequent mitochondrial dysfunction, disruption of mitochondrial dynamics, and oxidative stress can lead to cell death. Combination therapy of antibiotics with antioxidants has the potential to reduce the toxic effects of antibiotics. The negative effects of antibiotics on mitochondria can be put to good use by targeting harmful cell populations: cancerous, autoreactive lymphocytes.

Conflict of Interests

The author has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were used in the present research.

Informed Consent

The authors declare that no patients were used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors had equal roles in study design, work, statistical analysis and manuscript writing.

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