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Pharmacology

PHA 206

Bacteria

The four main mechanisms by which bacteria exhibit resistance to antibiotics are:

1.)Drug inactivation or modification: for example, enzymatic deactivation of penicillin G in some penicillin-resistant bacteria through the production of β-lactamases. Most commonly, the protective enzymes produced by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will reduce its ability to bind to the bacterial ribosomes and disrupt protein synthesis.

2.)Alteration of target- or binding site: for example, alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria. Another protective mechanism found among bacterial species is ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target the cell's ribosomes to inhibit protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to continue synthesizing proteins essential to the cell while preventing antibiotics from binding to the ribosome to inhibit protein synthesis.

3.)Alteration of metabolic pathway: for example, some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid.

Reduced drug accumulation: by decreasing drug permeability or increasing active efflux (pumping out) of the drugs across the cell surface.These pumps within the cellular membrane of certain bacterial species are used to pump antibiotics out of the cell before they are able to do any damage. They are often activated by a specific substrate associated with an antibiotic as in fluoroquinolone resistance.

4.)Ribosome splitting and recycling: for example, drug-mediated stalling of the ribosome by lincomycin and erythromycin unstalled by a heat shock protein found in Listeria monocytogenes, which is an homologous of HflX from other bacteria. Liberation of the ribosome from the drug allows further translation and consequent resistance to the drug.

B.)Viruses

Specific antiviral drugs are used to treat some viral infections. These drugs prevent viruses from reproducing by inhibiting essential stages of the virus's replication cycle in infected cells. Antivirals are used to treat HIV, hepatitis B, hepatitis C, influenza, herpes viruses including varicella zoster virus, cytomegalovirus and Epstein-Barr virus. With each virus, some strains have become resistant to the administered drugs.

Antiviral drugs typically target key components of viral reproduction; for example, oseltamivir targets influenza neuraminidase, while guanosine analogs inhibit viral DNA polymerase. Resistance to antivirals is thus acquired through mutations in the genes that encode the protein targets of the drugs.

Resistance to HIV antivirals is problematic, and even multi-drug resistant strains have evolved.One source of resistance is that many current HIV drugs, including NRTIs and NNRTIs, target reverse transcriptase; however, HIV-1 reverse transcriptase is highly error prone and thus mutations conferring resistance arise rapidly.Resistant strains of the HIV virus emerge rapidly if only one antiviral drug is used.Using three or more drugs together, termed combination therapy, has helped to control this problem, but new drugs are needed because of the continuing emergence of drug-resistant HIV strains.

C.) Fungi

Infections by fungi are a cause of high morbidity and mortality in immunocompromised persons, such as those with HIV/AIDS, tuberculosis or receiving chemotherapy.The fungi candida, Cryptococcus neoformans and Aspergillus fumigatus cause most of these infections and antifungal resistance occurs in all of them.Multidrug resistance in fungi is increasing because of the widespread use of antifungal drugs to treat infections in immunocompromised individuals.Fluconazole-resistant Candida species have been highlighted as a growing problem by the CDC.More than 20 species of Candida can cause Candidiasis infection, the most common of which is Candida albicans. Candida yeasts normally inhabit the skin and mucous membranes without causing infection. However, overgrowth of Candida can lead to Candidiasis. Some Candida strains are becoming resistant to first-line and second-line antifungal agents such as azoles and echinocandins.

D.) Parasites

The protozoan parasites that cause the diseases malaria, trypanosomiasis, toxoplasmosis, cryptosporidiosis and leishmaniasis are important human pathogens.

Malarial parasites that are resistant to the drugs that are currently available to infections are common and this has led to increased efforts to develop new drugs. Resistance to recently developed drugs such as artemisinin has also been reported. The problem of drug resistance in malaria has driven efforts to develop vaccines.

Trypanosomes are parasitic protozoa that cause African trypanosomiasis and Chagas disease (American trypanosomiasis).There are no vaccines to prevent these infections so drugs such as pentamidine and suramin, benznidazole and nifurtimox are used to treat infections. These drugs are effective but infections caused by resistant parasites have been reported.

Leishmaniasis is caused by protozoa and is an important public health problem worldwide, especially in sub-tropical and tropical countries. Drug resistance has "become a major concern".