16/MHS06/052

TOBORE OLOKOR

CO

PHM 302

Assignment

1. Write on a named bacterial protein synthesis inhibitor, stating its mechanism of action, indication for use, toxicity and adverse effects

Tetracyclines were discovered in the 1940s and exhibited activity against a wide range of microorganisms including gram-positive and gram-negative bacteria, chlamydiae, mycoplasmas, rickettsiae, and protozoan parasites. They are inexpensive antibiotics, which have been used extensively in the prophylaxis and therapy of human and animal infections and also at sub-therapeutic levels in animal feed as growth promoters. The first tetracycline-resistant bacterium, Shigella dysenteriae, was isolated in 1953. Tetracycline resistance now occurs in an increasing number of pathogenic, opportunistic, and commensal bacteria. The presence of tetracycline-resistant pathogens limits the use of these agents in treatment of disease. Tetracycline resistance is often due to the acquisition of new genes, which code for energy-dependent efflux of tetracyclines or for a protein that protects bacterial ribosomes from the action of tetracyclines. Many of these genes are associated with mobile plasmids or transposons and can be distinguished from each other using molecular methods including DNA-DNA hybridization with oligonucleotide probes and DNA sequencing. A limited number of bacteria acquire resistance by mutations, which alter the permeability of the outer membrane porins and/or lipopolysaccharides in the outer membrane, change the regulation of innate efflux systems, or alter the 16S rRNA. New tetracycline derivatives are being examined, although their role in treatment is not clear. Changing the use of tetracyclines in human and animal health as well as in food production is needed if we are to continue to use this class of broad-spectrum antimicrobials through the present century.

The tetracyclines, which were discovered in the 1940s, are a family of antibiotics that inhibit protein synthesis by preventing the attachment of aminoacyl-tRNA to the ribosomal acceptor (A) site. Tetracyclines are broad-spectrum agents, exhibiting activity against a wide range of gram-positive and gram-negative bacteria, atypical organisms such as chlamydiae, mycoplasmas, and rickettsiae, and protozoan parasites. The favorable antimicrobial properties of these agents and the absence of major adverse side effects has led to their extensive use in the therapy of human and animal infections. They are also used prophylactically for the prevention of malaria caused by mefloquine-resistant Plasmodium falciparum. Furthermore, in some countries, including the United States, tetracyclines are added at sub-therapeutic levels to animal feeds to act as growth promoters. Although the tetracyclines retain important roles in both human and veterinary medicine, the emergence of microbial resistance has limited their effectiveness. Undoubtedly the use of tetracyclines in clinical practice has been responsible for the selection of resistant organisms. Nevertheless, as we enter the new millennium, the use of tetracyclines and other antibiotics as animal growth promoters is becoming increasingly controversial because of concerns that this practice may be contributing to the emergence of resistance in human pathogens. The increasing incidence of bacterial resistance to tetracyclines has in turn resulted in efforts to establish the mechanisms by which genetic determinants of resistance are transferred between bacteria and the molecular basis of the resistance mechanisms themselves. The improved understanding of tetracycline resistance mechanisms achieved by this work has provided opportunities for the recent discovery of a new generation of tetracyclines, the glycylcyclines (see below). Further research, already under way, is also identifying approaches by which inhibitors of tetracycline resistance mechanisms might be developed for use in conjunction with earlier tetracyclines to restore their antimicrobial activity

MODE OF ACTION

It is well established that tetracyclines inhibit bacterial protein synthesis by preventing the association of aminoacyl-tRNA with the bacterial ribosome (44, 263). Therefore, to interact with their targets these molecules need to traverse one or more membrane systems depending on whether the susceptible organism is gram positive or gram negative. Hence, a discussion of the mode of action of tetracyclines requires consideration of uptake and ribosomal binding mechanisms. Also pertinent to this discussion are explanations of the joint antibacterial-antiprotozoal activity of the tetracyclines and the microbial selectivity of the class as a whole. Most of these issues have been considered at length in recent years (44, 67, 78, 263), so the focus here will be on new information.

Tetracyclines traverse the outer membrane of gram-negative enteric bacteria through the oomph and oomph porin channels, as positively charged cation (probably magnesium)-tetracycline coordination complexes (44, 263). The cationic metal ion-antibiotic complex is attracted by the Donnan potential across the outer membrane, leading to accumulation in the periplasm, where the metal ion-tetracycline complex probably dissociates to liberate uncharged tetracycline, a weakly lipophilic molecule able to diffuse through the lipid bilayer regions of the inner (cytoplasmic) membrane. Similarly, the electroneutral, lipophilic form is assumed to be the species transferred across the cytoplasmic membrane of gram-positive bacteria. Uptake of tetracyclines across the cytoplasmic membrane is energy dependent and driven by the ΔpH component of the proton motive force (192, 263). Within the cytoplasm, tetracycline molecules are likely to become chelated since the internal pH and divalent metal ion concentrations are higher than those outside the cell (263). Indeed, it is probable that the active drug species which binds to the ribosome is a magnesium-tetracycline complex (44, 144). Association of tetracyclines with the ribosome is reversible, providing an explanation of the bacteriostatic effects of these antibiotics (44).

Several studies have indicated a single, high-affinity binding site for tetracyclines in the ribosomal 30S subunit, with indications through photo-affinity labeling and chemical foot-printing studies that protein S7 and 16S rRNA bases G693, A892, U1052, C1054, G1300, and G1338 contribute to the binding pocket (44, 180, 196, 263). However, Schnappinger and Hillen (263) have pointed out that these apparent sites for drug interaction in the ribosome may not necessarily reflect the actual binding site. Indeed, interpretation of the probing studies referred to above is complicated by the observation that binding of tetracycline (which measures approximately 8 by 12 Å) to the ribosome appears to cause wide-ranging structural change in 16 S rRNA (193). Furthermore, photo-incorporation methods are subject to the limitation that upon irradiation, tetracycline photoproducts are generated which may react further with the ribosomes (196). Nevertheless, naturally occurring tetracycline-resistant propionibacteria contain a cytosine-to-guanine point mutation at position 1058 in 16S rRNA (251) (see below), which does at least suggest that the neighboring bases U1052 and C1054 identified by chemical foot-printing (180) may have functional significance for the binding of tetracyclines to the 30S subunit.

The absence of major antieukaryotic activity explains the selective antimicrobial properties of the tetracyclines. At the molecular level, this results from relatively weak inhibition of protein synthesis supported by 80S ribosomes (302) and poor accumulation of the antibiotics by mammalian cells (78). However, tetracyclines inhibit protein syntheses in mitochondria (221) due to the presence of 70S ribosomes in these organelles. It has been recognized for some time that the spectrum of activity of tetracyclines encompasses various protozoan parasites such as P. falciparum, Entamoeba histolytic-a, Guardia lambda, Leishmania major, Trichomonal vaginalis, and Toxoplasma gondii (28, 44, 67, 137, 214). The anti-parasitic activity is explained in some cases by the finding that certain organisms, e.g., P. falciparum, contain mitochondria (67). However, a number of other protozoa which lack mitochondria nevertheless remain susceptible to tetracyclines. At present there is no satisfactory molecular explanation for these findings (67).