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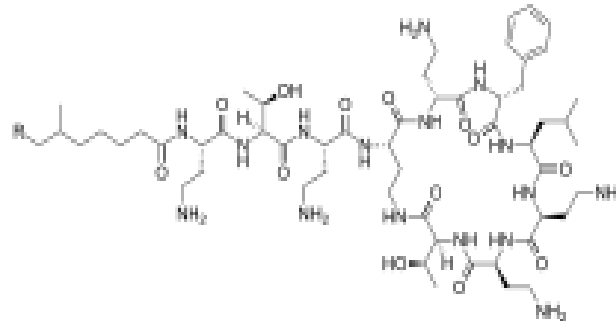
Inhibitors of Cytoplasmic Membrane Function

The cytoplasmic membrane that encompass all kinds of living cells perform a variety of vital functions , one of these selective permeability, carries out active transport functions, and thus controls the internal composition of the cell. If the functional integrity of the cytoplasmic membrane is disrupted, macromolecules and ions escape from the cell, and cell damage or death ensues. The cytoplasmic membrane of bacteria and fungi has a structure different from that of animal cells and can be more readily disrupted by certain agents. Consequently, selective chemotherapy is possible. The antibiotics classes that damage cell membranes have specificity for particular microbial groups, based on differences in the types of lipids in their cell membranes. The most important are the polymyxins, which act as detergents to dissolve bacterial cell membranes by binding to phospholipids present in the membranes .Other antibiotics ,like polyene antifungal (amphotericin B and nystatin) also act by binding to particular sterols present in the membranes of fungal cells. Polymyxins do not act on fungi ,and polyenes have no effect on bacteria .

Polymyxins

Polymyxins are antibiotics, with a general structure consisting of a cyclic peptide with a long hydrophobic tail. They disrupt the structure of the bacterial cell membrane by interacting with its phospholipids. They are selectively toxic for Gram-negative bacteria due to their specificity for the lipopolysaccharide molecule that exists within many Gram-negative outer membranes. Polymyxins found in forms A,B,C,D,E (B and E can be used therapeutically). Polymyxin B – derived from *Bacillus*

polymyxa var. *aerosporus* . Polymyxin E – derived from *Bacillus polymyxa* var. *colistinus*.(Colistin).All bactericidal.



structure of polymyxin

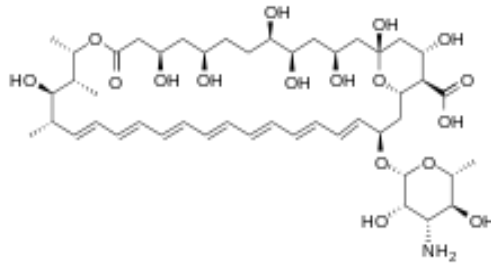
Mechanism of action

Polymyxins are positively charged molecules (cationic) which are attracted to the negatively charged bacteria. After binding to lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria, polymyxins alter the structure of membranes and make it more permeable. This disrupts osmotic balance causing leakage of cellular molecules, inhibition of respiration and increased water uptake leading to cell death. The hydrophobic tail is important in causing membrane damage, suggesting a detergent-like mode of action, and effects all membranes similarly. Toxic side effects are common. Polymyxins have little or no effect on Gram-positives since the cell wall is too thick to permit access to the membrane.

Amphotericin B

Amphotericin B is a polyene antifungal drug, often used intravenously for systemic fungal infections. It was originally extracted from *Streptomyces nodosus* ,a filamentous bacterium, in 1955.Its named originates from the chemical's amphoteric properties. Two amphotericins,

amphotericin A and amphotericin B are known, but only B is used clinically, because it is significantly more active *in vivo*.



structure of amphotericin

Mechanism of action

As with other polyene antifungals, amphotericin B binds with ergosterol, a component of fungal cell membranes, forming a transmembrane channel that leads to monovalent ion (K^+ , Na^+ , H^+ and Cl^-) leakage, which is the primary effect leading to fungal cell death.