

## **Lecture 13: Aminoglycosides**

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### **Knowledge Objectives**

1. Know the basic processes of bacterial protein synthesis.
2. Know the mechanism of antimicrobial activity for aminoglycosides.
4. Know the most common adverse effects.
5. Know the mechanisms of bacterial resistance.
6. Know the most common applications of these antibiotics for the treatment of disease. Which drugs are broad spectrum, and which have specific or unique uses.

### **Drug List**

#### **Aminoglycosides**

neomycin  
gentamicin  
streptomycin  
amikacin  
tobramycin  
kanamycin

## **Drugs inhibiting Protein Synthesis**

Aminoglycosides and Macrolides

Tetracycline and Chloramphenicol

## **Protein Synthesizing machinery**

### **Ribosome**

bacteria has 50S and 30 S subunit which forms 70 S  
polysome that slides on mRNA

has A, P and E sites for binding with tRNA

### **mRNA**

forms template for protein synthesis

transcribed from DNA

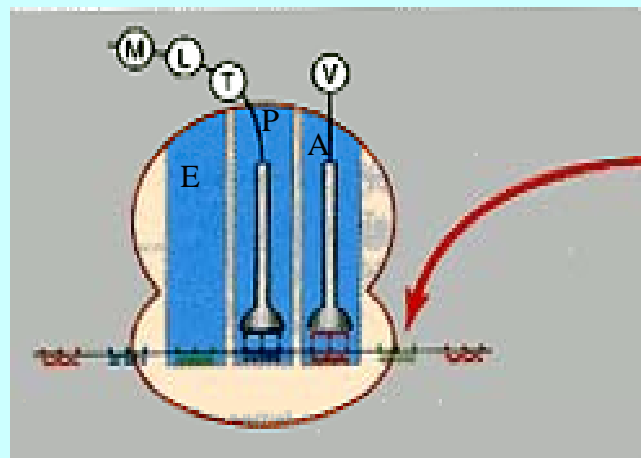
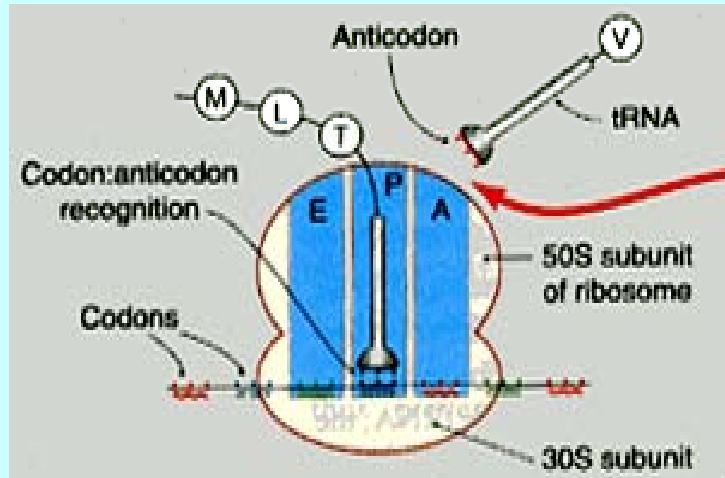
attaches to 30s ribosomes

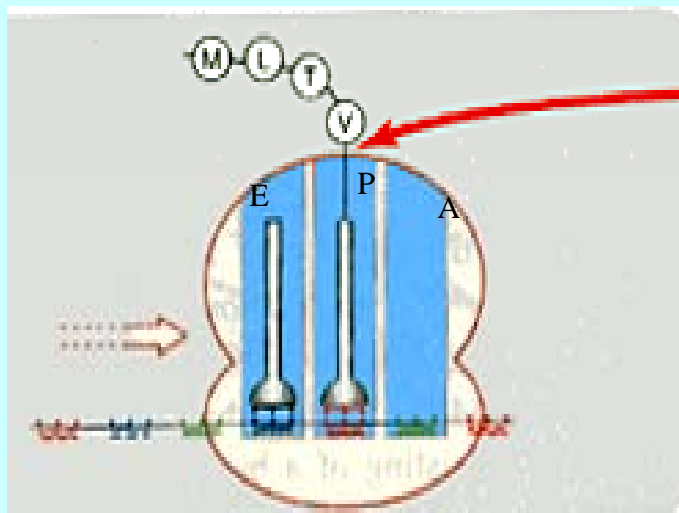
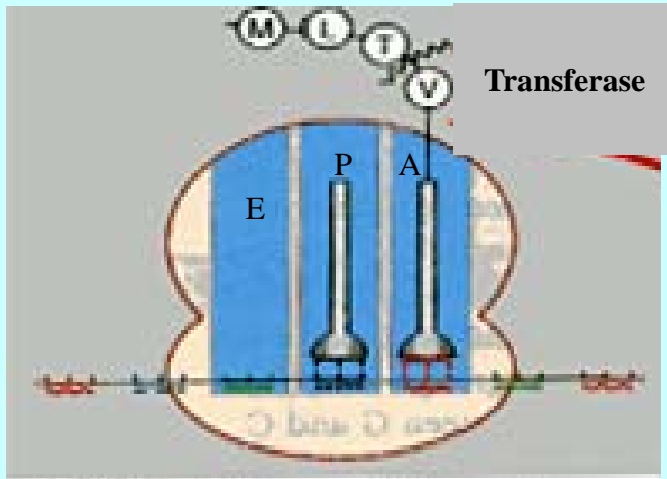
### **tRNA**

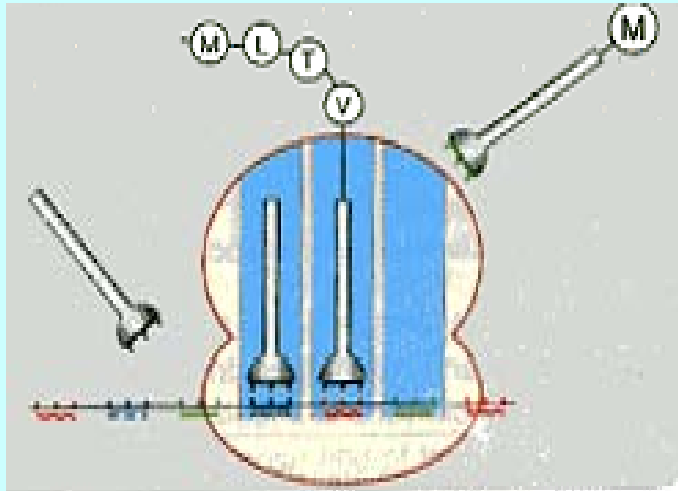
brings amino acids

attaches to A, P and E sites of ribosomes

**Overview:**







**Why antibiotic drugs do not inhibit mammalian protein synthesis??**

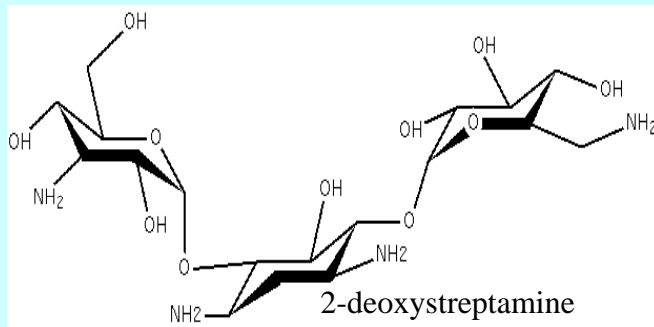
Eukaryotes : 60S and 40 S subunit

**Difference in ribosomal units is the basis of selectivity of antimicrobial drugs against bacteria**

## Aminoglycosides

Gentamicin  
Tobramycin  
Amikacin  
Netilmicin  
Kanamycin  
Streptomycin

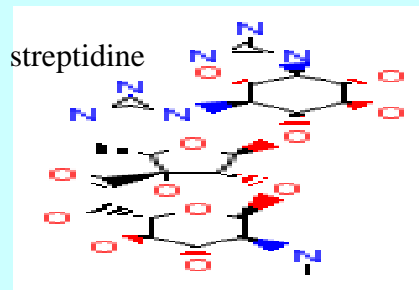
composed of amino-sugars  
water-soluble (hydrophilic)  
highly polarized



Kanamycin

Kanamycin A,B  
Tobramycin  
amikacin

Streptomycin



Bacterial killing → concentration dependent

Post-antibiotic effect persists after the serum conc < **minimum inhibitory concentration (MIC)**

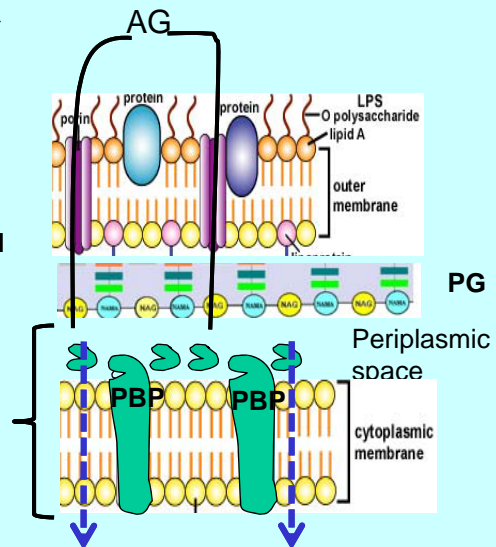
Once daily dose of aminoglycosides is therefore efficacious

## Aminoglycosides Entry

a. Diffusion through **porins**

b. Energy-Dependent Phase 1 (EDP1)

rate limiting requires  
negative inner membrane  
potential  
electron-transport chain

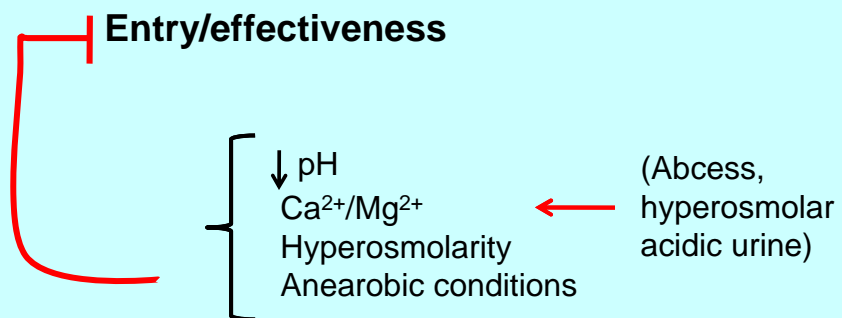


c) Create fissure inducing bacterial damage (**contrast from Tetra or Chloram**) further enhancing AG uptake (EDP2 phase)

Entry/effectiveness

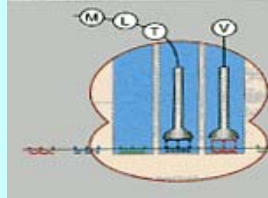
↓ pH  
Ca<sup>2+</sup>/Mg<sup>2+</sup>  
Hyperosmolarity  
Anearobic conditions

(Abscess, hyperosmolar acidic urine)



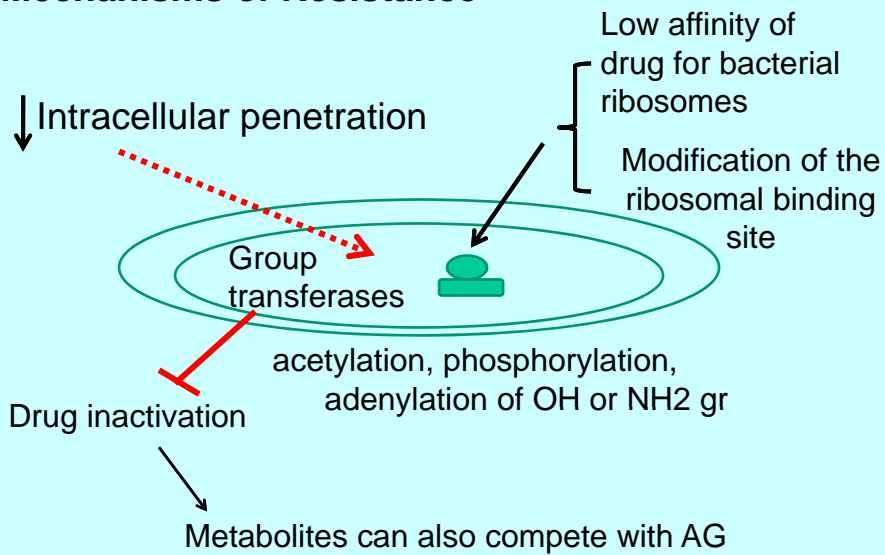
### Mechanism of Action:

a) binds to A site of 30s of ribosome subunit

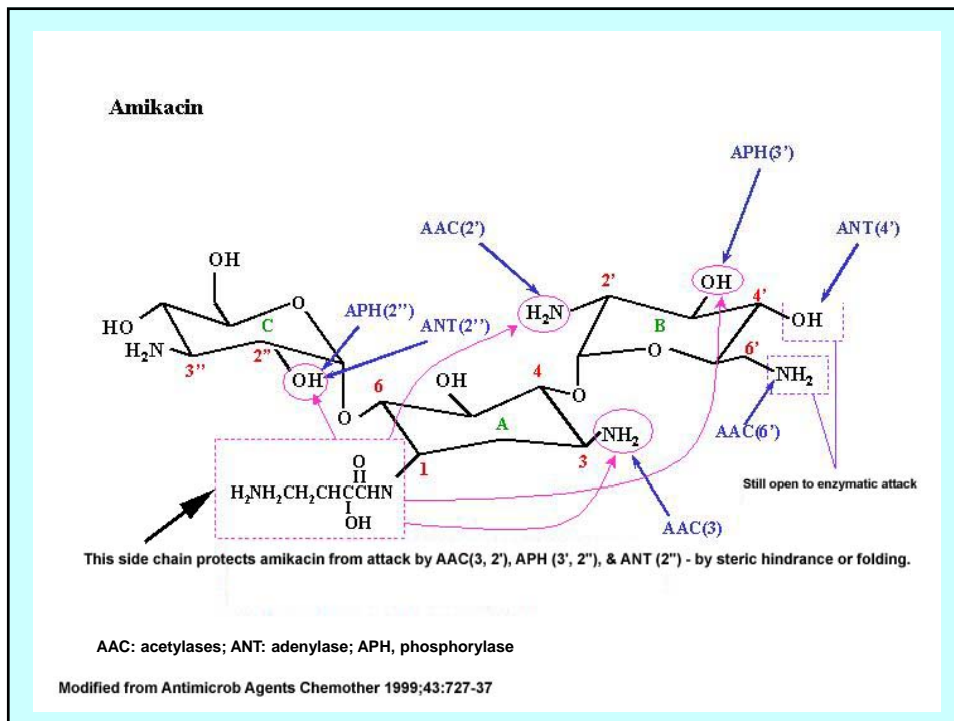


- i. interfere with the formation of the initiation complex
- ii. induce misreading of the mRNA template
- iii. Premature termination of mRNA translation
- iv. cause polysomes to break up into monosomes

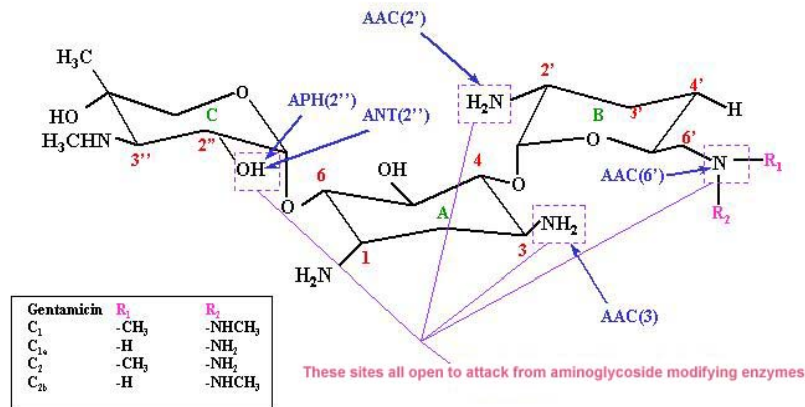
### Mechanisms of Resistance



Cross-resistance by other aminoglycosides  
 i.e. gentamicin → tobramycin, amikamicin, kanamycin and  
 netilmycin.  
 No effect on Steptomycin



## Gentamicin

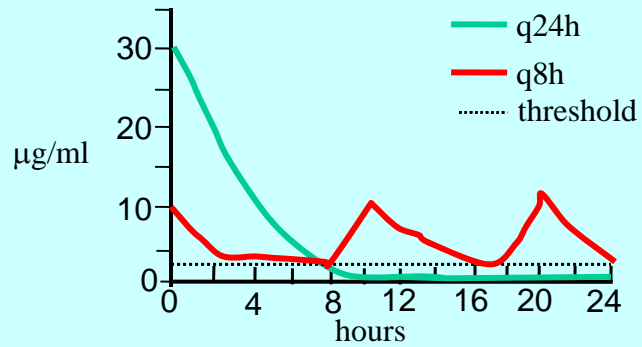


Modified from Antimicrob Agents Chemother 1999;43:727-37

## VI. Absorption

Oral or rectal administration: <1% of dose is absorbed

Rapidly absorbed from I.M; peak conc. in plasma occur after 30-90 min period 4-12 ug/ml following 1.5-2 mg/kg dose



Plasma concentrations after IV injection of 5.1 mg/kg to a hypothetical patient either as a single (q24h) or as three divided doses (q8h)

### **Distribution**

Do not cross BBB and do not achieve high distribution in body fluids.

**Can cross placenta**

## **Excretion**

Excreted entirely via the kidneys and urine conc of 50-200 ug/ml are achieved.

Clearance faster from plasma as compared to tissues

Clearance similar in adults and children older than 6 months; half life is prolonged in

The dosage must be adjusted for renal function.  
Should not be administered to patients in renal failure

## **V. Spectrum:**

**Aerobic** Gram (-) bacilli.

Kanamycin and Streptomycin: limited spectrum  
Should not be used for infections caused by Serratia or P.aeruginosa

1st -line drug for pseudomonas.

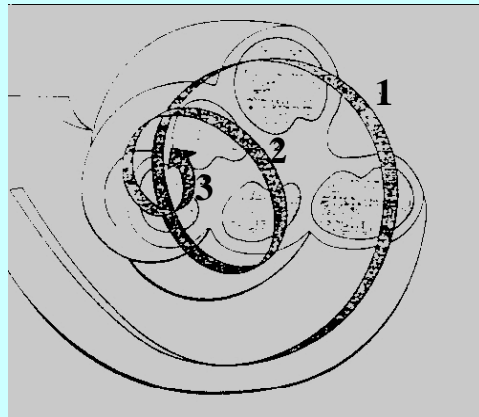
May be given with penicillin in infections caused by streptococci, Listeria sp.

**Anaerobic or facultative anaerobic** bacteria are resistant

## IX. Side Effects

**Ototoxicity (vestibular and auditory dysfunction)**

**Largely irreversible**



Cochlea, normally lined with hair cells that are destroyed by **high concentrations of aminoglycosides**. Aminoglycosides damage hair cells, especially in turn No. 1 and part of turn No. 2. Hairs are shed by the damaged cells to give loss of high-frequency response first (associated with turn No. 1) and low-frequency loss later (associated with turn to. 3).

amikacin, kanamycin, neomycin



cochlear damage



loss of high frequency tones

streptomycin and gentamicin



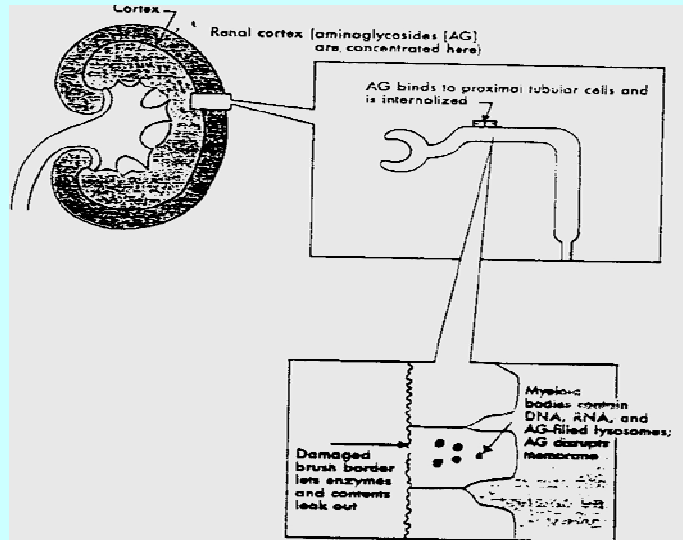
vestibular damage



loss of low frequency tones

Loop diuretics (furosemide and ethacrynic acid) potentiate the ototoxicity

## Rotoxicity (reversible)



mild rise in serum creatinine

proteinuria, casts

Leakage of enzymes-- alkaline phosphatase and aminopeptidase.

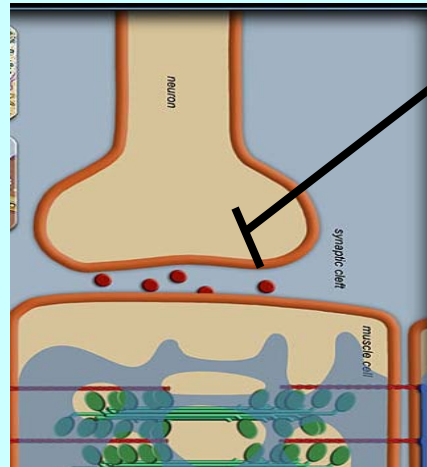
In severe cases, produces renal tubular necrosis

**Nephrotoxic potencies:** Neomycin > tobramycin  
= gentamicin > streptomycin

**antagonize** factor V resulting in bleeding

## Muscular blockade

(tobra<genta<amika<kana<neomy)



AG (curare-like)

**Caution:**  
Myasthenia gravis  
patients

**calcium gluconate or neostigmine** reverses this effect

## VII. Therapeutic Use:

### Streptomycin

unusual mycobacterial infections in combination  
with other antimicrobial agents (**toxic**)  
1000 mg/single or 500 mg double dose → serum  
concentration of 50-60 and 15-30 hg/ml

### Tuberculosis

### Plague

Bacterial endocarditis (strep + Penn G) replaced by  
(genta + PennG)

**Tularemia** (Strep or Genta)

**Gentamicin: *Ist choice; low cost, and reliable***  
***activity agnst all*** Gram (-) bacilli including infections  
caused by pseudomonas aeruginosa

IT or IV: used rarely as cuases local inflammation

**$\beta$ -lactum-insensitive UTI's**

Bacterial endocarditis

**Sepsis**

**Topical as in burn patients**

**Tobramycin (Tobrex) (~ Gentamicin)**

## **Amikacin**

Broadest spectrum, absobed rapidly after IM injection;  
Peak plasma concentration ~20ug/ml after 7.5 mg/kg  
injection

**Nosocomial Gram (-) infections**

**Netilmicin~Gentamicin**

can be used for Gentamicin resistant bacteria

**Neomycin:**

frequently used in topical ointments;  
administered oral to clean the bowel prior to  
bowel surgery (not absorbed, eliminated in the  
feces, very toxic if administered I.M.)

### **Summary: Aminoglycosides**

Requires **oxygen** and changes in transmembrane potential to act on 30S ribosome

Most toxic; **ototoxicity, rototoxicity, muscular blockade**, conc in serum should be monitored

Limited spectrum **Gram(-) Aerobes**

**ineffective in anaerobes**

**will work in facultative bact in aerobic environment**

Use diminished as other Antibiotics became available

Use for historical dis: **Plague, TB**