

EXOTOXINS

- Bacterial protein toxins are the most potent poisons may show activity at very high dilutions.
- Protein toxins are resemble enzymes.
- bacterial exotoxins are:
 - ✓ Proteins.
 - ✓ Denatured by heat, acid, proteolytic enzymes.
 - ✓ Have a high biological activity (most act catalytically).
 - ✓ Exhibit specificity of action.
 - ✓ Bacterial exotoxins have enterotoxic, cytotoxic, hemolytic and neurotoxic effect.

Features of Exotoxins

- Exotoxins:
 - Excreted by living cells
 - Produced by Gram-positive and Gram-negative bacteria
 - Polypeptides
 - Usually bind to specific receptors on cells
 - Highly toxic. Fatal to animals in very small doses

- Relatively heat labile. Toxicity destroyed over 60°C
- Highly antigenic. Stimulate formation of antitoxin. Antitoxin neutralizes the toxin
Converted to toxoid by formalin. Toxoid is nontoxic but antigenic used to immunize, e.g. tetanus toxoid
- Usually controlled by extra-chromosomal genes, e.g. plasmids, phage gene
- do not produce fever in the host

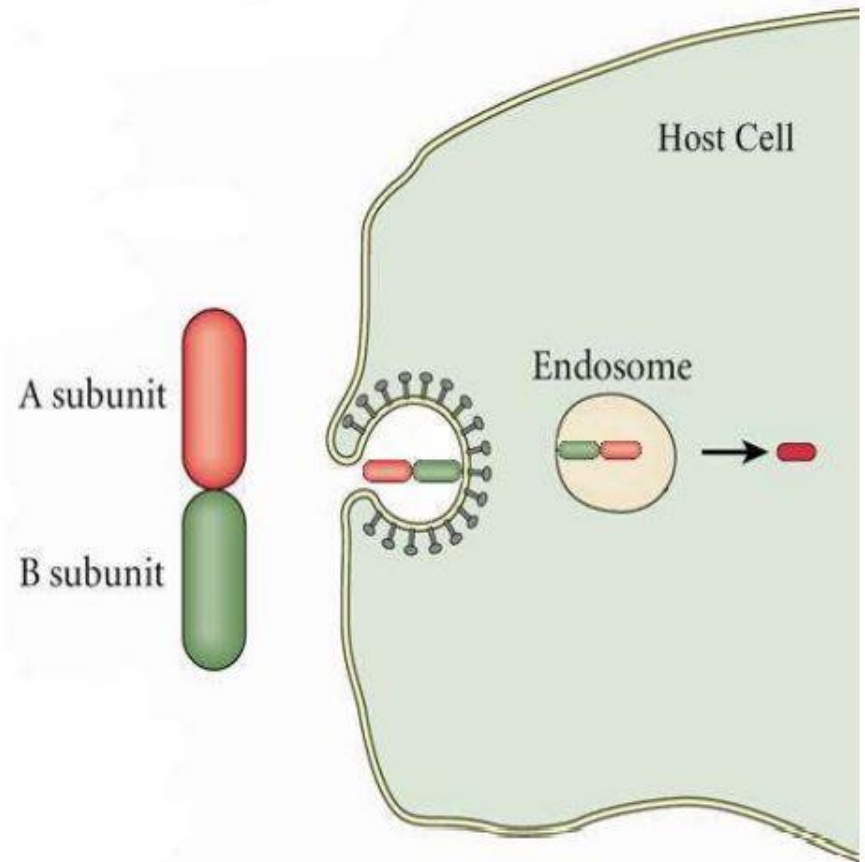
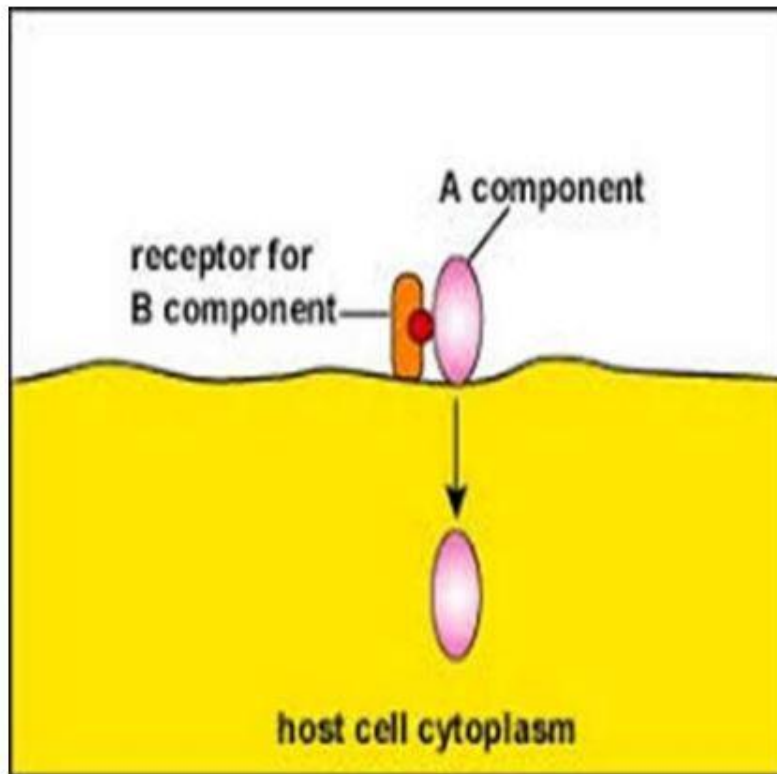
A+B subunit arrangement

- Many protein toxins, notably those that act intracellularly (with regard to host cells), consist of two components:
- One component (subunit A) is responsible for the enzymatic activity of the toxin;
- The other component (subunit B) is concerned with binding to a specific receptor on the host cell membrane and transferring the enzyme across the membrane.
- The enzymatic component is not active until it is released from the native (a+b) toxin.

Attachment and Entry of Toxins

- There are at least two mechanisms of toxin entry into target cells.
- Direct entry, the b subunit of the native (a+b) toxin binds to a specific receptor on the target cell and induces the formation of a pore in the membrane through which the a subunit is transferred into the cell cytoplasm.
- Alternative mechanism : receptor-mediated endocytosis (rme).

Attachment and entry of toxin



Bacteria produced exotoxin

Name of bacteria	Name of exotoxin	Type of action
<i>Staphylococcus. Aureus</i>	Enterotoxin, toxic shock syndrome	Acts as super antigen, stimulates T- cell ,releases large amount of cytokines
<i>Streptococcus.pyogenus</i>	S.Pyrogenic exotoxin	Acts as super antigen, stimulates T- cell ,releases large amount of cytokines
<i>Corynebacterium.diphtheriae</i>	Diphtheria toxin	Inhibiting protein synthesis by inhibiting Elongation Factor-2
<i>Clostridium.perfringens</i>	Alpha-toxin	Lecithinase and phospholipase activity causes myo-necrosis
<i>Clostridium.tetani</i>	Tetanus toxin (tetanospmin)	Decreases the neurotransmitter, release from the inhibitory neurons(glycine&GABA)
<i>Clostridium.botulinum</i>	Botulinum toxin	Decrease neuro transmitter (acetyl- choline) release from neurons (spastic- paralysis)
Escherichia.coli (diarrheagenic)	Heat – labile toxin	Act.of adenylate cyclase ↑ cAMP in target cell diarrhea
	Heat-stable	↑ cAMP in target cell secretory diarrhea
	verocytotoxic	Inhibiting protein synthesis by inhibiting ribosomes
Shigella dysentriae type 1	Shiga toxin	Inhibition of protein synthesis by inhibiting of ribosomes
Vibrio cholerae	Cholera toxin	Act.of adenylate cyclase ↑ cAMP in target cell diarrhea
pseudomonas	Exotoxin	Inhibiting protein synthesis by inhibiting Elongation Factor-2

Staphylococcal enterotoxin

- It is responsible for the manifestations of staphylococcal food poisoning: nausea, vomiting and diarrhoea 2-6 hrs after consuming food contaminated by toxin.
- Toxin is relatively heat stable, resisting 100°C for 10-40 mins depending on the concentration of the toxin and the nature of the medium.
- About 2/3rd of *S. aureus* strains, growing in carbohydrate and protein foods, secrete the toxin.
- Milk and milk products are also contaminated.
- The source of infection is usually a food handler, who becomes a carrier.

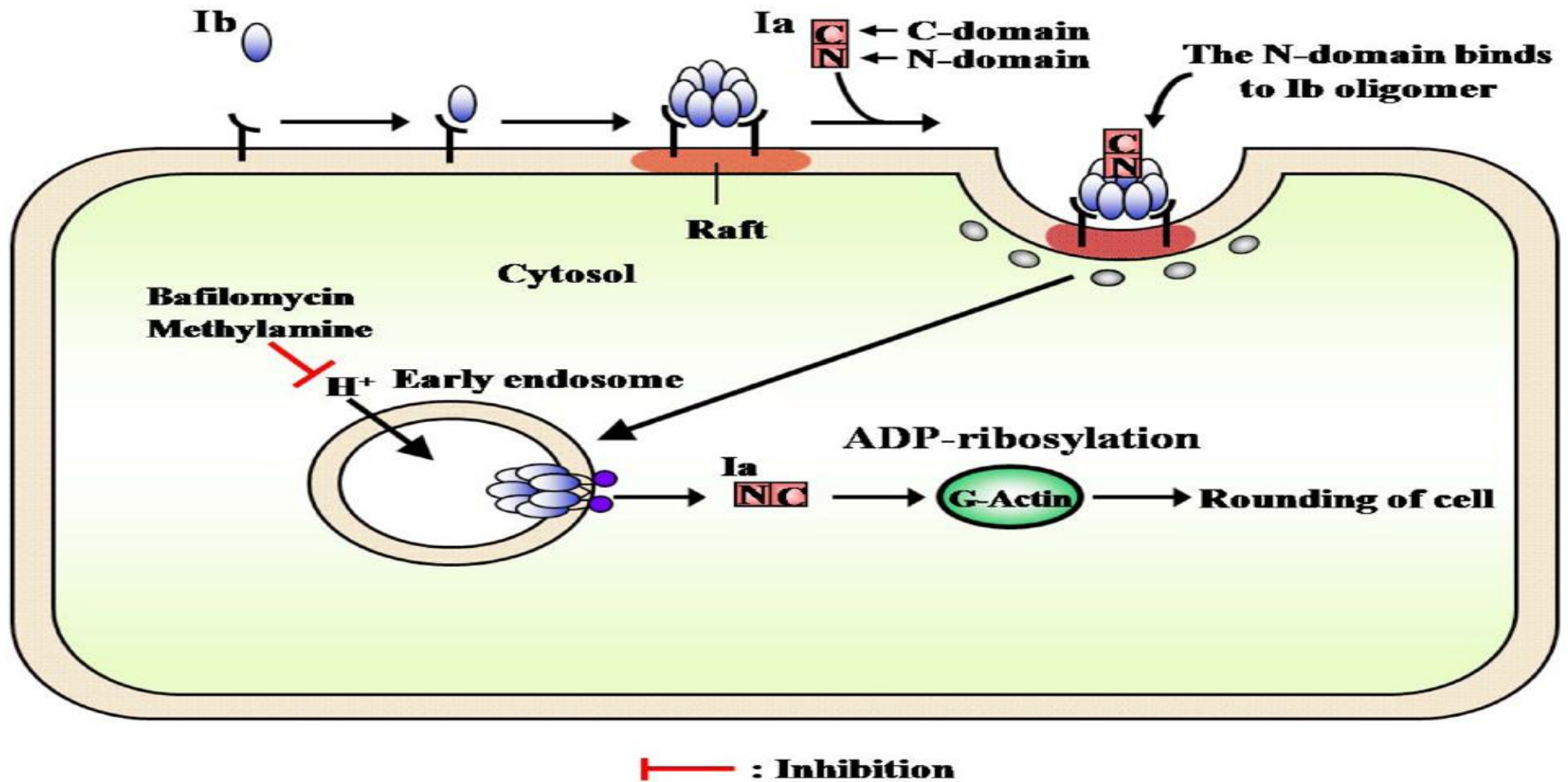
- 8 antigenic types of enterotoxins are currently known, named A,B,C1- 3, D,E and H. they are formed by toxigenic strains either by singly or in combination.
- The toxin acts directly on autonomic nervous system to cause illness.
- The toxin is very potent.
- The toxin also exhibit pyrogenic, mitogenic, hypotensive, thrombocytopenic and cytotoxic effect.
- Sensitive serological tests such as latex agglutination and ELISA are available for detection of toxin.

Toxic shock syndrome

- It is potentially fatal multisystem disease presenting with fever, hypotension, myalgia, vomiting, diarrhea, mucosal hyperaemia and an erythematous rash.
- TSST type 1 is often more responsible, though enterotoxin B or C may also cause the syndrome.
- TSST 1 antibody seen in convalescents.
- Staphylococcal enterotoxins and TSST-1 are super antigens which are potent activators of T lymphocytes.
- This leads to an excessive and dysregulated immune response, with release of cytokines interleukin1-2, TNF and interferon gamma.
- This explains the multisystem involvement and florid manifestations in staphylococcal food poisoning and TSS.

Clostridium perfringens Toxin

- **Perfringolysin O:**
- Cholesterol-dependent cytolysins (CDCs) constitute a family of pore forming toxins secreted by Gram positive bacteria.
- These toxins form transmembrane pores by inserting a large β -barrel into cholesterol-containing membrane bilayers.
- Binding of water-soluble CDCs to the membrane triggers, formation of oligomers containing 35-50 monomers.
- The coordinated insertion of more than seventy β -hairpins into the membrane requires multiple structural conformational changes and leads to pore formation.
- Perfringolysin O (PFO), secreted by *Clostridium perfringens*, has become the prototype for the CDCs.



- ❖ Clostridium perfringens iota-toxin is composed of the enzyme component (Ia) and the binding component (Ib).
- ❖ Ib binds to receptor on targeted cells and translocates Ia into the cytosol of the cells.
- ❖ Ia ADP-ribosylates actin, resulting in cell rounding and death