Review

Mechanisms of staphylococcal enterotoxin-induced emesis

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ABSTRACT

Pathogenic bacteria use various strategies to interact with the host organisms. Among them, toxin production constitutes an efficient way to alter specific functions of target cells. Various enterotoxins interact with the enteric nervous system, by stimulating afferent neurons or inducing neurotransmitter release from enterochromaffin cells which result either in vomiting, diarrhea, or in the intestinal inflammation process. *Staphylococcus aureus* produces a wide variety of toxins including staphylococcal enterotoxins (SEs) with demonstrated emetic activity; and staphylococcal enterotoxin-like (SEl) proteins, which are not emetic in a primate model or have yet to be tested. SEs and SEls have been traditionally subdivided into classical (SEA to SEE) and new (SEG to SElX) types. These toxins possess superantigenic activity and are highly resistant to denaturation which allows them to remain intact in contaminated foods and trigger food poisoning outbreaks. Symptoms are of rapid onset, and include nausea and violent vomiting. SEA is the most recognizable toxin causing food poisoning in humans throughout the world. However, it remains unclear how SEs induce emesis and via which signal pathway. This review is divided into four parts, and will focus on the following: (1) how bacterial toxins interact with the nervous system, (2) biological characteristics of SEs and SEls, (3) mechanisms of SE-induced emesis, and (4) use of a vaccine for the prevention of SE-induced emesis.

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1. Introduction

Pathogenic bacteria utilize multiple approaches to establish infection, food poisoning and to induce toxicity in eukaryotic cells. Various pathogens employ their toxins to modify host's homeostasis. Most toxins are multifunctional and have the ability to recognize and injure a wider range of cell including intestinal epithelial cells, neuronal cells, hepatocytes and lymphocytes, and thus allow the pathogen access to nutrients. Bacterial exotoxins often target specific cells. For instance, enterotoxins interfere with intestinal epithelial cells (Popoff, 1998), whereas neurotoxins act on neuronal cells leading to neurological symptoms. Bacterial toxins can act locally at the infectious site and/or at the systemic level through circulation, and are responsible for severe diseases in both humans and animals. Bacterial toxins can recognize specific cell surface receptor(s) and/or specific intracellular target(s). When bound to a receptor, toxins can unleash their toxic effects at the cell membrane by interfering with signal transduction pathways, pore formation, or enzymatic activities in the cell membrane (Lubran, 1988). In contrast, some toxins can enter the cytosol, recognize, and modify specific downstream intracellular targets (Lubran, 1988). Intracellularly active toxins cause a dramatic alteration in cellular functions including protein synthesis, cell homeostasis, cell cycle progression, vesicular trafficking, and/or actin cytoskeletal rearrangement. According to the nature of toxin and the type of target cells, toxins can trigger necrosis or apoptosis in various cell types including neuron. In contrast, some extracellularly active toxins exclusively interact with neuron from the central or peripheral nervous system inducing specific neurological symptoms. Various enterotoxins interact with the enteric nervous system by stimulating afferent neurons or induce neurotransmitter release from enterochromaffin cells which result in vomiting, diarrhea, or intestinal inflammation. Some toxins can pass through the blood–brain barrier and directly act on specific neurons (Caleo and Schiavo, 2009). This review focuses on the pathogenicity of bacterial toxins interacting with nervous system, mainly on staphylococcal enterotoxins (SEs) produced by *Staphylococus aureus*. Initially we describe the general properties of the bacterial toxins and their interaction with nervous system and consequent diseases. Next, we discuss in detail structures, and biological characteristics of SEs, as well as their mechanism of induction of emesis. Subsequently, we introduce a vaccine for the prevention of SE-induced emesis.

2. Bacterial toxins interacting with the nervous system

Some toxins cause pore formation after recognizing ubiquitous membrane components as receptors, such as cholesterol, gangliosides, and proteins. Two unique classes of neurotoxins, botulinum toxin and tetanospasmin, have evolved as specific inhibitors of the neuroexocytotic machinery. These toxins recognize specific receptors on neuronal cells and only interfere with highly specialized intracellular molecules that play a pivotal role in evoked release of neurotransmitters (Caleo and Schiavo, 2009). In addition, bacterial enterotoxins can interact with enterocytes and amplify their intestinal activity by stimulating the secretomotor reflex via the enteric nervous system (ENS), or interact with vagal afferents leading to vomiting (Farthing, 2000). It is noteworthy that the ENS is a preferential target for various bacterial toxins, which transit through the intestinal tract.

2.1. Toxins affecting nerve cell inhibition and excitation

Botulinum toxins produced by *Clostridium botulinum* are very potent neurotoxins and are responsible for neurological disorders in both humans and animals (Humeau et al., 2000; Lalli et al., 1999; Meunier et al., 2002; Popoff and Poulain, 2010). Botulinum toxins may enter by oral route or they can be produced directly in the intestine subsequent to intestinal colonization of *C. botulinum* which then undergo a transcytosis across the digestive mucosa (Ahsan et al., 2005; Couesnon et al., 2008; Jin et al., 2009; Maksymowych and Simpson, 1998, 2004; Matsumura et al., 2008). These toxins can target numerous neurons, as well as non-neuronal cells at high concentrations, inhibiting the release of various neurotransmitters including acetylcholine, glutamate, gamma aminobutyric acid (GABA), dopamine, serotonin (5-hydroxytryptomine, 5-HT), substance P, and glycine (Dunant et al., 1987; Foran et al., 2003; McMahon et al., 1992; Najib et al., 1999; Neale et al., 1999; Poulain et al., 1988; Sanchez-Prieto et al., 1987; Smith et al., 2005).

Tetanospasmin produced by *Clostridium tetani* is also potent neurotoxin, which is responsible for neurological disorders in humans and animals. Botulinum toxins and tetanospasmin display a similar intracellular mechanism of action, although they use different routes. Tetanospasmin diffuses in the extracellular fluid and can target many types of nerve endings, but it is mainly retrogradely transported through motoneurons. It inhibits the regulated release of glycine and GABA and disrupts the negative control exerted by the inhibitory interneurons onto motoneurons turning on excessive firing of the motoneurons and ensuing muscle contraction (Deinhardt et al., 2006; Schiavo et al., 2000).

Tetanospasmin and botulinum toxins are translocated in different subset of neurons, produce strongly different symptoms and clinical signs (tetanospasmin: spastic paralysis; botulinum toxins: flaccid paralysis). These toxins are representative bacterial toxins that affect inhibition and excitation of nerve cells.

2.2. Toxins inducing diarrhea

Increasing evidence suggests that some enterotoxins mediate diarrhea not only by acting directly upon enterocytes, but also by interfering/stimulating the enteric nervous system (Pothoulakis et al., 1998). Cholera toxin (CT) produced by *Vibrio cholerae* is a pathogenic toxin of a serious epidemic disease characterized by severe diarrhea and dehydration (Asakura and Yoshioka, 1994). CT consists of single A subunit and five B subunits assembled in a pentamer. CT recognizes the glycosphingolipid GM1 on enterocyte membrane, which then is internalized into endocytic vesicles (De Haan and Hirst, 2004). The A fragment of CT is responsible for the enzymatic activities of the toxin, including NAD hydrolysis in ADP-ribose and nicotinamide, and covalent transfer of ADP-ribose to Arg-187 of the subunit of stimulatory protein Gs leading to stimulation of adenylate cyclase and elevated intracellular cAMP (De Haan and Hirst, 2004). The increased cAMP induces activation of protein kinase A, which subsequently phosphorylates numerous substrates in the cell. This results in an active Cl^- secretion and a decrease in NaCl-coupled absorption by enterocytes (De Haan and Hirst, 2004). CT can also stimulate 5-HT release from enterochromaffin cells primarily localized at the base of the epithelial crypts of the intestine, probably via its effect on adenylate cyclase activation (Lundgren, 1998; Turvill et al., 1998).

Heat-labile enterotoxin (LT) produced by *Escherichia coli* is another well known toxin that induces diarrhea in humans and animals. LT does not stimulate the release of 5-HT from enterochromaffin cells, and the diarrhea induced by LT is not inhibited by 5-HT- or substance P-receptor antagonists (Farthing, 2000). However, lignocaine and the ganglionic blocker, hexamethonium, have a preventive effect, suggesting that the ENS is also involved in the enteric activity of LT, but via a distinct pathway than that mediated by 5-HT (Farthing, 2000; Turvill et al., 1998). The heat-stable enterotoxin (ST) from *E. coli* activates guanylate cyclase,