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Review Article

Military potential of biological toxins

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AFB, aflatoxins B
STEC, Shiga toxin-producing *Escherichia coli*
STX, saxitoxin
TTX, tetrodotoxin
BTX, batrachotoxins

ABSTRACT

Toxins are produced by bacteria, plants and animals for defense or for predation. Most of the toxins specifically affect the mammalian nervous system by interfering with the transmission of nerve impulses, and such toxins have the potential for misuse by the military or terrorist organizations. This review discusses the origin, structure, toxicity and symptoms, transmission, mechanism(s) of action, symptomatic treatment of the most important toxins and venoms derived from fungi, plants, marine animals, and microorganisms, along with their potential for use in bioweapons and/or biocrime. Fungal trichothecenes and aflatoxins are potent inhibitors of protein synthesis in most eukaryotes and have been used as biological warfare agents. Ricin and abrin are plant-derived toxins that prevent the elongation of polypeptide chains. Saxitoxin, anatoxin, and tetrodotoxin are marine-derived toxins that bind to sodium channels in nerve and muscle tissue and cause muscle paralysis. Most bacterial toxins, such as botulinum and Shiga affect either the nervous system (neurotoxins) or damage cell membranes. Batrachotoxins, which are secreted by poison-dart frogs are extremely potent cardiotoxic and neurotoxic steroidal alkaloids. The aim of this review is to provide basic information to enable further understanding of these toxins and their potential military uses.

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Introduction

Many potent toxins are nature compounds produced by microorganisms, plants, and animals. T-2 toxin (also known ''Yellow Rain'') is one of the most toxic trichothecenes and is thought to have been used in 1980s as a chemical weapon in Southeast Asia (Desjardins, 2009). Aflatoxins are known to have been weaponized by Iraq (so-called ''cancer bombs'') (Paterson, 2006). Most of bacterial toxins are large proteins that affect either the nervous system (neurotoxins) or damage cell membranes. Ricin, another potent toxin named ''compound W'' by the British military, as incorporated into a bomb; however, the ''W-bomb'' has never actually used (Crompton and Gall, 1980). Marine-derived toxins (such as anatoxins, saxitoxin (STX) and tetrodotoxin (TTX)) have the potential for use in terrorist-designed biological weapons, but are unlikely to pose a major threat in an open battlefield situation (Franz, 1996). The use of toxins as weapons may increase in the future because they are highly effective and can be used surreptitiously.

Understanding the mechanism(s) underlying toxicity is the first step to developing medical countermeasures. Toxins fall into two broad categories, as follows: (a) neurotoxins, which affect nervous system function (most often the peripheral nervous system) and the effect of which are typically temporary and/or reversible; and (b) membrane-damaging toxins, which destroy or damage tissues or organs either directly or indirectly via the release of secondary mediators. The effects of membrane-damaging toxins are often not reversible (Franz, 1996).

Understanding the global profile of these toxins is very important for health and risk assessment; however, military toxins have never been fully evaluated. The difference between conventional chemical weapons and biological warfare agents has been discussed by Madsen (2001). Bigalke and Rummel (2005) and Anderson (2012) discussed the use of tirchothecenes, ricin, and botulinum neurotoxins and Dixit et al. (2005) reviewed many neurotoxins; however, little was mentioned regarding detailed mechanisms of action, transmission and possible treatments. Pita (2009) authored an interesting article about the use of toxins as meapons from World War I to the present day.

Here, we will discuss the major toxins derived from fungi, plants, marine animals and frogs along with their venoms in spite of their origin, structure, toxicity and symptoms, transmission, mechanism(s) of action, symptomatic treatment, and their potential use for bioweapons.

Fungal toxins

Fungal toxins are low molecular weight compounds (<1000 g/mol) produced by fungi. The potential use of fungal toxins as weapons or ''expressions of discontent'' is taken very seriously because they can be used by governments or by small groups of individuals. For example, an individual could use such a toxin to carry out a revenge attack on an employer (Paterson, 2006). Indeed, trichothecene mycotoxins and aflatoxins are thought to have been used as biological warfare agents.

Trichothecene (T-2) mycotoxin

Origin

T-2 toxin as one of the primary members of type-A trichothecenes is produced mainly by *Fusarium* genus. The most important producer is *Fusarium sporotrichioides*, a saprophyte (Moss, 2002). T-2 toxin has been recognized as an unavoidable contaminant in cereals such as wheat, barley, oats, maize, and animal feed (Guan et al., 2009).

T-2 toxin is associated with several diseases in animals and humans. Alimentary toxic aleukia (ATA), a typical disease for human, is found to be associated primarily with the ingestion of moldy cereal infected with T-2 toxin (Joffe, 1974). Due to its high toxicity and stability, T-2 toxin is classified as biological weapon (Kuca and Pohanka, 2010).

Chemical structure

Trichothecenes are tetracyclic sesquiterpenoid compounds harboring a C-12-C-13-epoxy group. The trichothecene skeleton (scirpene) comprises a pyran group, a C-12-C-13-epoxide ring, and a double (olefinic) bond at C-9-C-10. Trichothecenes are grouped into four categories (A–D) based on their structural characteristics. T-2 and HT-2 toxins belong to group A, which is characterized by a functional group other than a carbonyl at C-8 (Wu et al., 2010, 2011). The chemical structures of the trichothecenes are shown in Fig. 1.

Trichothecenes are nonvolatile compounds with a molecular weight between 250 and 550 Da. They are relatively insoluble in water but highly soluble in organic solvents such as acetone, ethyl acetate, chloroform, and dimethylsulfoxide. Trichothecene compounds are stable when exposed to air and/or light, but they can be degraded by the presence of bacteria and fungi. Trichothecenes are not inactivated by autoclaving, but are deactivated by strongly acidic or alkaline conditions and by heating to 900 °F (482 °C) for 10 min or to 500 °F (260 °C) for 30 min (Wannenmacher and Wiener, 1997; Sudakin, 2003).

Toxicity and symptoms

Trichothecenes are toxic to humans, animals, and plants (Wannenmacher and Wiener, 1997). Their acute toxicity varies with animal species and/or the route of administrations. The LD_{50} value of T-2 toxin in rats and rabbits is 0.85 ± 0.03 and 1.10 ± 0.08 mg/kg body weight, respectively (Chan and Gentry, 1984). Acute exposure to weapons containing trichothecene mycotoxins is a major concern for those working in the filed of military medicine (Wannenmacher and Wiener, 1997). Early symptoms and signs included severe nausea, vomiting, superficial skin discomfort (burning sensation), lethargy, weakness, dizziness, and loss of coordination. Diarrhea (first watery brown and later grossly bloody) begins within minutes to hours after exposure. From 3 to 12 h post-exposure, the victim suffers dyspnea, coughing, sore mouth, bleeding gums, epistaxis, hematemesis, abdominal pain, and central chest pain. The exposed cutaneous areas become red, tender, swollen, painful, or pruritic. Small or large vesicles and bullae might form, and petechiae, ecchymoses, and black leathery areas of necrosis may appear. After death, the necrotic areas slough easily when the corpse is moved (Wannenmacher and Wiener, 1997).