Advanced Drug Delivery Reviews 90 (2015) 81–100

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Polymer antidotes for toxin sequestration☆

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ARTICLE INFO

Available online 27 May 2015

Keywords:
Synthetic polymers
Venom
Antidotes
Anti-venom
Toxin sequestration

ABSTRACT

Toxins delivered by envenomation, secreted by microorganisms, or unintentionally ingested can pose an immediate threat to life. Rapid intervention coupled with the appropriate antidote is required to mitigate the threat. Many antidotes are biological products and their cost, methods of production, potential for eliciting immunogenic responses, the time needed to generate them, and stability issues contribute to their limited availability and effectiveness. These factors exacerbate a world-wide challenge for providing treatment. In this review we evaluate a number of polymer constructs that may serve as alternative antidotes. The range of toxins investigated includes those from sources such as plants, animals and bacteria. The development of polymeric heavy metal sequestrants for use as antidotes to heavy metal poisoning faces similar challenges, thus recent findings in this area have also been included. Two general strategies have emerged for the development of polymeric antidotes. In one, the polymer acts as a scaffold for the presentation of ligands with a known affinity for the toxin. A second strategy is to generate polymers with an intrinsic affinity, and in some cases selectivity, to a range of toxins. Importantly, *in vivo* efficacy has been demonstrated for each of these strategies, which suggests that these approaches hold promise as an alternative to biological or small molecule based treatments.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Current and Forthcoming Approaches for Systemic Detoxification".

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http://dx.doi.org/10.1016/j.addr.2015.05.011
0169-409X/

1. Introduction

Antidotes are substances that counteract toxin poisoning. In situations where the toxin is introduced as a result of a venomous bite or sting, successful treatment often requires administration of antivenom in a timely manner. Unfortunately, a majority of incidents occur in remote locations that preclude rapid intervention and as a result, mortality rates are high. Antivenom is typically a biological product. The active components of antivenom are polyclonal antibodies which bind to and neutralize the venom, halting further damage. Injecting venom into a large mammal elicits an immune response, producing antibodies against the venom's active component(s). The antibodies are harvested from the animal's blood, and following purification, the sera containing antibodies is administered intravenously for treatment. Despite the fact that biological antivenoms are the only effective, approved treatment available, their cost, methods of production, potential for eliciting immunogenic responses, the time needed to generate them, and their stability are areas that can be improved.

Toxin poisoning is also a significant concern during infections of pathogenic bacteria. Many bacteria secrete protein and peptide toxins that are important virulence factors that contribute to the pathogenicity of the organism. Antibiotics are the standard defense against bacterial diseases. However, targeting virulence factors rather than the bacteria themselves offers several potential advantages. Since antivirulence therapies are not directed at bacteria themselves, there is less evolutionary pressure to induce antibiotic resistant strains. In addition, non-antibiotic treatments do not disrupt the normal microbiome that is typically associated with antibiotic treatments [1]. Use of antivirulence therapies would reduce the medical complications that may arise from the reduction of these healthy organisms [2–4]. In addition to suppressing pathogenicity, development of non-antibiotic, antivirulence agents may contribute to our understanding of these mechanisms and offer opportunities to devise new approaches to inhibit bacterial toxins.

Synthetic polymer antidotes may be useful as alternatives to polyclonal antibodies in antivenom and as antivirulence agents. There are a number of reasons polymer antidotes can provide an attractive alternative to biological antitoxins. Polymers can be synthesized rapidly and inexpensively in the chemistry laboratory. Since they are abiotic, their composition is easier to control and they have a substantially lower risk of eliciting an immunogenic response due to biological contamination. Most synthetic polymers are inherently more robust than proteins. Like some antivenoms they can be freeze dried and stored compactly as powders. However, being abiotic, they can have a considerably longer shelf life than protein based biological antitoxins and are much less sensitive to thermal shock. The multigene families that encode the toxins of venomous animals and bacteria are actively selected on, thus isoforms of biological toxins readily evolve from the same species. Although polymer antidotes may lack the specificity of some biological antibodies, their ability to neutralize multiple isoforms of a toxin may allow a broader therapeutic efficacy.

This review is concerned with synthetic polymers that are designed, evaluated, or have potential for use as antidotes against toxins. The range of toxins covered includes plant, animal and bacteria toxins. Although strictly speaking, toxins are of biological origin, similar challenges face the development of polymeric heavy metal sequestrants for use as antidotes to heavy metal poisoning, so recent findings in this area have also been included. Polymers capable of sequestering biological toxins have been included in a number of reviews [5–7], but these discussions were generally limited to selected polymers or toxins. Here we provide a more comprehensive evaluation of polymeric systems reported to be useful in neutralizing toxins. The concept of polymeric constructs being used as antidotes is still in its infancy. Nevertheless, a wide range of strategies have emerged that may have promising medical applications. One common strategy to impart polymers with affinity to toxins is to decorate the synthetic polymer with ligands that have known affinity to the target toxin. The affinity ligands can range from proteins, peptides, oligosaccharides, and synthetic small molecule inhibitors. The presentation of these ligands on polymeric scaffolds generates multivalent interactions which generally enhance toxin inhibition. An alternative strategy is the synthesis of polymers that, on the basis of their chemical composition alone, have an intrinsic affinity for a target toxin or biomolecule. In each of these strategies advances in polymer synthesis allow “polymer engineering” to control size, chemical composition and architecture. These attributes can be modulated to achieve affinity, selectivity and efficacy against different classes of toxins. In the following sections we review a number of toxins for which polymeric sequestrants have been developed and examine the polymer attributes that contribute to toxin neutralization.

2. Polymer materials for venom neutralization

2.1. Introduction

Venom is a complex mixture of enzymes, polypeptides, and small molecules that have evolved as a biological weapon meant to neutralize attackers or prey. The composition of most venom is diverse and may include cytotoxins, hemotoxins, neurotoxins, and myotoxins. The exact composition of an animal's venom may be dependent on a number of factors such as its genealogy, diet, and age. The diversity of venom makes treatments difficult to develop. However, a few polymeric systems have emerged that have shown promise in neutralizing the cytotoxic components of some venoms. The chemical composition of these polymers has been rationally designed to have an intrinsic affinity for the target cytotoxin. Also, in some cases a molecular imprinting approach was implemented to generate binding sites with both affinity and specificity in the polymer architecture. The investigation of polymers to sequester venom or its components has been limited, but the following examples provide evidence that further research into polymeric antidotes for envenomation may yield materials that could serve as alternatives to current biological antivenoms.

2.2. Melittin

Melittin (Mel), a cytolytic 26 amino acid peptide, is the principal component of honey bee venom (Fig. 1). Mel is a prototypical membrane-damaging toxin that creates unregulated pores in the membrane of cells. These toxins do not exert their biological activity by directly interacting with a specific receptor, but rather by a mechanism that involves association with cell membranes. The lack of a specific receptor interaction increases the difficulty of developing a therapeutic strategy to inhibit these toxins. An effective strategy would be to sequester Mel during circulation thereby inhibiting access of Mel to the cell membrane. Antibodies, such as those found in antivenom, provide such an alternative. Antibodies rely on noncovalent complimentary interactions between the chemical functional groups of the target molecule and the variable antigen-binding domain of the antibody. To mimic this