First characterization of immunogenic conjugates of Vi-negative Salmonella Typhi O-specific polysaccharides with rEPA protein for vaccine development

Muhammad Salman

Abasyn University, Pakistan

Abstract

Efficacious typhoid vaccines for young children will significantly reduce the disease burden in developing world. The Vi polysaccharide based conjugate vaccines (Vi-rEPA) against Salmonella Typhi Vi-positive strains has shown high efficacy but may be ineffective against Vi-negative S. Typhi. In this study, for the first time, we report the synthesis and evaluation of polysaccharide-protein conjugates of Vi-negative S. Typhi as potential vaccine candidates. Four different conjugates were synthesized using recombinant exo-protein A of Pseudomonas aeruginosa (rEPA) and human serum albumin (HSA) as the carrier proteins, using either direct reductive amination or an intermediate linker molecule, adipic acid dihydrazide (ADH). Upon injection into mice, a significantly higher antibody titer was observed in mice administrated with conjugate-1 (OSPHSA) (P=0.0001) and conjugate 2 (OSP-rEPA) (P≤0.0001) as compared to OSP alone. In contrast, the antibody titer elicited by conjugate 3 (OSPADH-HSA) and conjugate 4 (OSPADH-rEPA) were insignificant (P=0.1684 and P=0.3794, respectively). We conclude that reductive amination is the superior method to prepare the S. Typhi OSP glycol-conjugate. Moreover, rEPA was a better carrier protein than HSA. Thus OSP-rEPA conjugate seems to be efficacious typhoid vaccines candidate, it may be evaluated further and recommended for the clinical trials.

Introduction

Vaccine development and usage over the years has significantly reduced the number of infections and diseases. Improved knowledge of immune protection and a big leap in genetic engineering has allowed the induction of a variety of new types of vaccines through the manipulation of DNA, RNA, proteins, and sugars. Creation of attenuated mutants, expression of potential antigens in live vectors, and purification and direct synthesis of antigens in new systems have immensely improved vaccine technology. Both infectious and non-infectious diseases are now within the realm of vaccinology. The profusion of new vaccines has enabled the targeting of new populations for vaccination as well as the cure and removal of infectious agents from their natural reservoirs. Still, as with ancient infections like malaria and new infections like HIV, a potent vaccine is elusive, which poses a big challenge to the scientific world. For the purposes of this chapter, the process of vaccine research and development (R&D) is described as if the process occurs in an ordered, chronological fashion. In this somewhat simplified view, vaccine research begins only after a careful assessment of public health priorities. Work conducted in the basic research laboratory forms the scientific foundation for all subsequent investigation. Applied R&D then moves to the clinical research setting, and from there to pilot production and full-scale manufacture. The vaccine must then be purchased, distributed, and used. Finally, a surveillance system is established to monitor immunization coverage, efficacy, and any adverse health effects related to vaccine administration. The surveillance system also may detect fluctuations in disease incidence or new disease entities requiring a realignment of public health priorities.

In reality, the stages of vaccine development are not so neatly divided. For instance, although basic research is the starting point, it does not end when applied R&D begins; basic research findings continue to inform the process of vaccine development, even during clinical testing. Likewise, findings at the applied and clinical levels feed observations and questions back to the basic research laboratory. From the standpoint of disease control, making vaccines available is only the first step in ensuring adequate levels of immunization. For example, to receive the full benefit of vaccines, children must be immunized at specific times throughout infancy and into early adolescence. In a perfect world, every parent would keep track (or be notified by a health-care worker) of his or her child's immunization status and would make sure that the child received the needed vaccinations on time. This frequently does not happen in practice, however; indeed, as outlined in Chapter 2, many children in the United States under age 2 are underimmunized. Some experts have suggested that the United States establish a computerized national vaccine registry (Freeman et al., 1993; Johnson, 1991), which allows for more efficient follow-up and notification of children who need vaccination by requiring uniform reporting. A national vaccine registry is proposed in congressional legislation (S. 732). In addition, the CDC is currently developing state-based plans for tracking immunication coverage (Walter Orenstein, Division of Immunization, Centers for Disease Control and Prevention, personal communication, 1993). Computerized tracking systems are likely to require large investments in new equipment and training and considerable behavioral changes among private health-care providers and the public at large.

For reasons that are not fully understood, vaccines that are very effective in preventing disease among infants in the industrialized world appear to be less efficacious in infants in different epidemiological settings. For example, both live oral polio vaccine and measles vaccine, both of which are comparable to effective products licensed in the United States, have tended to be less effective when used in areas highly endemic for these diseases, particularly in the developing world.