Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Review

Adjuvants for vaccines to drugs of abuse and addiction

Carl R. Alving[a,*], Gary R. Matyas[a], Oscar Torres[a,b], Rashmi Jalah[a,b], Zoltan Beck[a,b]

[a] Laboratory of Adjuvant and Antigen Research, US Military HIV Research Program, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA
[b] U.S. Military HIV Research Program, Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Bethesda, MD 20817, USA

ARTICLE INFO

Article history:
Received 13 May 2014
Received in revised form 15 July 2014
Accepted 29 July 2014
Available online xxx

Keywords:
Adjuvants
Immunotherapeutic vaccines
Morphine
Heroin
Cocaine
Nicotine
Methamphetamine
Oxycodone
Hydrocodone

ABSTRACT

Immunotherapeutic vaccines to drugs of abuse, including nicotine, cocaine, heroin, oxycodone, methamphetamine, and others are being developed. The theoretical basis of such vaccines is to induce antibodies that sequester the drug in the blood in the form of antibody-bound drug that cannot cross the blood brain barrier, thereby preventing psychoactive effects. Because the drugs are haptens a successful vaccine relies on development of appropriate hapten-protein carrier conjugates. However, because induction of high and prolonged levels of antibodies is required for an effective vaccine, and because injection of T-independent haptenic drugs of abuse does not induce memory recall responses, the role of adjuvants during immunization plays a critical role. As reviewed herein, preclinical studies often use strong adjuvants such as complete and incomplete Freund's adjuvant and others that cannot be, or in the case of many newer adjuvants, have never been, employed in humans. Balanced against this, the only adjuvant that has been included in candidate vaccines in human clinical trials to nicotine and cocaine has been aluminum hydroxide gel. While aluminum salts have been widely utilized worldwide in numerous licensed vaccines, the experience with human responses to aluminum salt-adjuvanted vaccines to haptenic drugs of abuse has suggested that the immune responses are too weak to allow development of a successful vaccine. What is needed is an adjuvant or combination of adjuvants that are safe, potent, widely available, easily manufactured, and cost-effective. Based on our review of the field we recommend the following adjuvant combinations either for research or for product development for human use: aluminum salt with adsorbed monophosphoryl lipid A (MPLA); liposomes containing MPLA [L(MPLA)]; L(MPLA) adsorbed to aluminum salt; oil-in-water emulsion; or oil-in-water emulsion containing MPLA.

1. Introduction

A worldwide epidemic of use and abuse of addictive drugs is responsible for massive, socially disruptive, and still increasing medical, social, economic, and political problems, and is associated with widespread suffering, including high risks of morbidity, disability, and death [1]. Among young injection drug users in San Francisco between 1997 and 2007 overall mortality rates were 10 times higher than those in the general population [2]. Use of addictive drugs is also associated with many diseases that vary in type and prevalence in different populations. For example, prevalence of HIV-1 infection among injection drug users in Argentina from 1987 through 1999 ranged from 27% to 80% [3]. According to the United Nations Office On Drugs And Crime [4]: "of the estimated 16 million injecting drug users worldwide, UNODC estimates that almost one in five is HIV-positive. Approximately the same proportion are infected with hepatitis B, whereas some 8 million – about half of all injecting drug users – are infected with hepatitis C."

Current pharmacologic methods for treatment of individuals suffering from substance abuse often have problems of high cost, limited availability, compliance difficulties, diversion of opiate agonists such as methadone, and the inefficiency that patients often have high relapse rates [5]. Because of these many problems innovative alternative therapeutic approaches are being explored, and vaccines may represent a unique and potentially attractive supplemental approach that could be useful for treatment of chemical addiction. Some of the drugs of abuse that are current targets for experimental therapeutic vaccines include: opiates, such as heroin and morphine; stimulants such as cocaine and methamphetamine; prescription pain-killers such as hydrocodone and oxycodone; and general use chemicals such as nicotine, a widely used addictive drug which has complex stimulatory and social effects [6–9].

* Corresponding author. Tel.: +1 301 319 7449; fax: +1 301 319 7518.
E-mail address: calving@hivresearch.org (C.R. Alving).

http://dx.doi.org/10.1016/j.vaccine.2014.07.085
0264-410X/

What is the mechanism by which addictive drugs work, and how would a vaccine work? In the course of typical drug use, crude or partially refined chemicals are introduced into the blood of the user, and the active chemical must then cross the blood–brain barrier in order to exert psychoactive effects by binding to an appropriate receptor in the brain. Repeated injections of psychoactive drugs have varying degrees of physical and psychological reinforcing effects that often lead to addiction. The theoretical strategy for a creating a therapeutic vaccine to an offending drug lies in the induction of high levels of specific antibodies that capture the drug in the blood to prevent the drug from crossing the blood–brain barrier, thus blocking the psychoactive effect. A further important aspect of the dynamics of drug abuse is that the reinforcing actions of intravenously administered drugs are usually directly related to the speed of infusion. Thus, even if antibodies to the drug could only retard the rate of transport of the drug from the blood to the brain a beneficial effect would still be achieved [5]. Therefore, an effective vaccine could work either by complete sequestration of the drug in the blood, or by serving as a "pharmacokinetic antagonist" to slow the speed of entry of the drug into the brain, either of which approaches would result in a diminished psychoactive effect [5].

2. Immunogenicity of drugs and the need for adjuvants

The challenge to production of antibodies to addictive drugs is that the drugs are haptens, i.e., substances that are not immunogenic by themselves. The term hapten, originally introduced as a concept by Landsteiner in the 1920s and 1930s, was defined functionally as a small chemical entity that cannot induce antibodies by itself but which can induce specific binding antibodies upon conjugation to a protein [10]. A more succinct modern definition is that a hapten is a small functional group corresponding to a single antigenic determinant [11,12].

The demonstration by Landsteiner that numerous types of small molecular weight natural and synthetic chemicals and drugs could serve as haptens [10] led to a long history of creation of polyclonal antisera containing specific antibodies as reagents for analytic and diagnostic immunoassays for drugs, including assays for drugs of abuse [13–20]. Antisera that were used for immunoassays were routinely obtained by immunizing animals with a protein-hapten conjugate that was emulsified with complete Freund's adjuvant usually followed by immunization with the conjugated protein-hapten emulsified with either complete or incomplete Freund's adjuvant. Freund's adjuvants are both water-in-oil (w/o) emulsions in which the stabilizing emulsifier (usually mannide monooleate) causes tiny droplets of water to be stabilized and distributed throughout the larger bulk oil phase [21,22]. This general immunizing procedure has now resulted in development of a large number of clinical immunoassays that utilize either polyclonal or monoclonal antibodies for detection of many other types of haptenic drugs [23,24].

With the validation from the initial studies that conjugates of proteins with small synthetic chemicals and drugs could serve as antigens to induce specific antibodies, efforts began in the 1970s to explore the possibility that animals immunized with protein-morphine conjugates emulsified with Freund's adjuvant could serve as models for in vivo blocking of the psychoactive effects of morphine [25]. As described below, the tradition of immunization of animals with Freund's adjuvant to obtain therapeutic antisera to drug haptens has persisted to this day. However, it is well known that complete Freund's adjuvant is unacceptable for human use. Although incomplete Freund's adjuvant, and similar w/o adjuvants, have been used extensively for a variety of prophylactic and therapeutic human vaccines [26,27], they are not currently considered to be at the forefront of modern vaccine adjuvants because of potential toxicities [28,29].

2.1. The need for adjuvants for immunization against drugs of abuse

"Behind every great vaccine is a great adjuvant [but] behind a great adjuvant may be an outdated carrier protein" [8]. This cautionary remark by Janda and Treweek is a reminder that chemical and formulation strategies for vaccines to haptenic drugs require a combination of creative synthetic organic chemistry for obtaining surrogate haptens, use of suitable carrier proteins, conjugation of the surrogate hapten to the carrier, and formulation of the conjugate with a safe and powerful adjuvant to induce high levels and long duration of high quality antibodies to the offending drug. In the quest for development of candidate vaccines to morphine, heroin, cocaine, methamphetamine, oxycodone, nicotine, and similar addictive drugs, a wide variety of adjuvants and carrier proteins has been employed in various studies to immunize different species of experimental animals as well as humans [8,30]. Table 1 provides a broad perspective of the different adjuvants that have been employed both for obtaining antibodies for clinical immunoassays and for research on candidate vaccine formulations in animals and humans.

What is an adjuvant? In this context, a vaccine adjuvant has been defined by the European Medicines Agency (EMEA) in a regulatory guideline as "a component that potentiates the immune responses to an antigen and/or modulates it toward the desired immune responses. An active ingredient of a combined vaccine that has an adjuvant effect on other active ingredients of the vaccine is excluded from the scope of this Guideline. Also excluded are carriers for haptens, antigens (e.g., CRM197, meningococcal OMP, tetanus toxoid and diphtheria toxoid that are used to conjugate polysaccharides) and excipients such as HAS" [67]. In the guideline EMEA also lists 25 specific examples of adjuvants that are arranged in six categories.

The above EMEA guideline covers only adjuvants in vaccines against infectious diseases, including those containing hapten-like oligosaccharides linked to carrier proteins as antigens. However, from a theoretical standpoint small synthetic chemicals probably pose greater complexity than oligosaccharides as haptens for vaccines because, unlike carbohydrates which are naturally present as complex polysaccharides on the surfaces of bacterial particles during infection [68,69], injected chemicals are soluble in plasma and are not attached to infectious particles during repeated injections. Because of this, repeated injections of a therapeutic vaccine will be required in order to maintain high levels of binding antibodies to the drug during the course of therapy for withdrawal from drug abuse. The need for potent adjuvants for induction of antibodies is emphasized by the observation that as many as one-third to two-thirds of patients vaccinated with candidate vaccines to drugs of abuse fail to achieve a sufficient antibody response [32,36–38]. This could have been due to the development of low affinity IgM antibodies during the course of drug use which results in suppression of induction of high affinity IgG by the anti-drug vaccine, or it could have reflected an idiosyncratic inability of a subset of individuals to produce high levels of antibodies or, more likely, it could have been due to low potency of the aluminum salt adjuvant that was used.

2.2. Types of adjuvants and adjuvant strategies

The purpose of this review is to examine the various types of adjuvants that have been used, and to present the rationales for utilization and optimization of modern adjuvants, or combinations of adjuvants, for candidate vaccines. The field of preclinical

Please cite this article in press as: Alving CR, et al. Adjuvants for vaccines to drugs of abuse and addiction. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.07.085