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Immunotherapy for Drug Abuse

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Abstract

Substance use disorders continue to be major medical and social problems worldwide. Current medications for substance use disorders have many limitations such as cost, availability, medication compliance, dependence, diversion of some to illicit use and relapse to addiction after discontinuing their use. Immunotherapies using either passive monoclonal antibodies or active vaccines have distinctly different mechanisms and therapeutic utility from small molecule approaches to treatment. They have great potential to help the patient achieve and sustain abstinence and have fewer of the above limitations. This review covers the cocaine vaccine development in detail and provides an overview of directions for developing anti-addiction vaccines against the abuse of other substances. The notable success of the first placebo-controlled clinical trial of a cocaine vaccine, TA-CD, has led to an ongoing multi-site, Phase IIb clinical trial in 300 subjects. The results from these trials are encouraging further development of the cocaine vaccine as one of the first anti-addiction vaccines to go forward to the U.S. Food and Drug Administration for review and approval for human use.

Keywords

Substance use disorders; immunotherapies; vaccine; cocaine; TA-CD

INTRODUCTION

Substance use disorders (SUD) have significant personal consequences for affected persons and their families, as well as causing negative medical, psychological, and social outcomes for society at large [1]. Treatment providers use a combination of pharmacotherapy and behavioral therapies to help patients successfully enter and maintain recovery and thereby address these multiple morbidities [2, 3]. Preventing relapse and maintaining recovery has become a focus of long-acting medications. Medications that can be administered infrequently (perhaps once a month or less) while helping the patient remain abstinent or at least freedom from relapse to full abuse and dependence are increasingly considered the keystone of long-term rehabilitation for SUD patients.

Immunotherapies have great potential as long-acting agents to prevent relapse by blocking the effects of the abused drugs. These immunotherapies can be administered as either passive monoclonal antibodies or as active vaccines and both formulations are potentially important and currently being researched [4–6]. These biologicals represent yet another

frontier in the ongoing quest for novel pharmacological strategies that could be integrated into comprehensive treatment programs to reduce substance use and establish abstinence. Ultimately, immunotherapies and vaccines shift our conceptualization of drugs of abuse as “foreign” substances that we can target using the body's own defenses against such substances. The incredible specificity and potency of these self-defenses can be more effective blockers than any small chemical compounds that we have developed against these abused drugs. The basic immunological approach that we used for developing the cocaine vaccine illustrated in detail in this paper also has been directed to several other abused substances to create blocking agents. Only the simple molecule of alcohol defeats these self-engineered therapies, because alcohol is simply too small (two carbons) and too ubiquitous in the body to allow the formation of antibodies against it.

ANTIBODY ACTIONS IN BLOCKING ABUSED DRUGS

Drugs of abuse lead to reward and reinforcement by attaching to neuronal receptors on very specific brain pathways, and antibodies prevent those drugs from accessing these brain pathways in a manner that can produce reinforcement. After entering the body *via* any route, abused substances rapidly enter the brain to activate target neurotransmitter systems by binding to specific receptors or neurotransmitter transporters. The small molecular size of these abused drugs allows them to rapidly traverse the blood-brain barrier, and once in the brain to diffuse quickly to their binding sites, where they also act very quickly to stimulate dopamine activity in the pathway leading to the nucleus accumbens. Dopamine may be released directly from the ventral tegmental area neurons or indirectly through stimulation of this common general pathway of reinforcement, thus augmenting the addictive process [7].

Antibodies are meant to capture the abused drug before it can cross the blood-brain barrier, thereby preventing activation of the brain's reinforcement pathways, and thus blunting or eliminating the addictive liability of a substance. This simple “sponge” model of antibodies has much merit and probably describes a significant component of their actions, but these antibodies do more than just act as a sponge that can indefinitely soak up the abused drugs since the total number of antibody binding sites is necessarily limited, and not every drug molecule of a bolus dose can be tightly bound. This additional action of the antibodies relates to their pharmacokinetic properties as buffers against the rapid transit of abused drugs into the brain. Antibodies in circulation rapidly establish an equilibrium of bound and free drug in concentrations dependent on how tightly the antibodies can bind the drug molecules [4–6]. Thus small amounts of the substance may diffuse into tissues, including the brain, but the rapid accumulation from the bolus dose is prevented. This kinetic buffering may be ultimately more important than their sponge action based on various studies in both animals and humans. A critical human observation to illustrate this kinetic point is that smoked and intravenous cocaine administration with their very rapid delivery of cocaine to the brain within seconds is highly reinforcing, and sparked an epidemic of abuse when smoked crack cocaine replaced marketing of cocaine powder for intranasal administration [8]. Moreover, oral cocaine requires considerably larger doses to be as reinforcing as the intravenous route of administration [9]. This need for an increased dose in part reflects that oral cocaine reaches the brain relatively slowly, and although high blood and brain levels can be attained, much higher levels are needed to produce euphoria or other reinforcing effects [10–12]. The kinetic effects of a pool of antibodies in circulation may act in a similar way by slowing drug entry into the brain and reducing the reinforcing effects of this drug.

How are these antibodies produced? The fundamental concept is to create a new macromolecular compound, which the body will recognize as a foreign antigen that requires an immune response. Drugs of abuse by themselves are far too small to elicit such immune responses from B and T cells of the immune system, so their presentation to the body and its

immune processes must be profoundly changed. This profound change in the presentation is the purpose of a conjugate vaccine. Such a vaccine is simply a combination that chemically links the abused drug to a large immunogenic protein such as inactivated tetanus or cholera toxin [13]. Both of these proteins are vaccines on their own and have been widely used throughout the world for over 40 years to prevent these infectious diseases. Moreover, the concept of linking them or similar large immunogenic proteins to small molecules called haptens in order to produce an antibody response is not new and was pioneered in the 1970s as a treatment approach to digitalis toxicity and about the same time as a morphine vaccine [14–16].

In contrast to the passive immunization with polyclonal horse serum in the digitalis overdose treatment, antidrug vaccines are active immunizations, where administration of the vaccine triggers an immunological response against the agent in the human subject [17–20]. Immunological memory is created, whereby re-exposure to the agent (i.e., through a booster injection) results in amplification of the initial response. This contrasts with passive immunization using polyclonal or monoclonal antibodies where no immunological memory is formed, and when the antibody levels fall, the antibodies themselves must be administered again. Because the immune system has been primed by active vaccination, later introduction of the agent results in the production of an antigen-specific, immunoglobulin G (IgG)-mediated antibody response. The effectiveness of the vaccine is then measured by its ability to create antibodies with specificity and high binding affinity for the drug of abuse and the robustness of the antibody response, i.e., the concentration of antibody produced [21].

BRIEF HISTORY OF HAPTENATED VACCINES FOR ADDICTIONS

In 1972 Berkowitz and colleagues [15] developed a morphine vaccine in animals. Using rats, they administered a morphine hapten linked to bovine serum albumin (a carrier protein) and created antimorphine antibodies. These antibodies reduced the concentration of free morphine in the plasma of their vaccinated rats. A later study was done soon after by other investigators who created a similar vaccine in primates, and the vaccinated rhesus monkey primates decreased their self-administration of heroin [16]. However, this heroin vaccine development stopped abruptly in the mid-1970s as methadone maintenance spread rapidly across the country as an outpatient treatment of choice for both patients and providers [22]. Furthermore, an oral, small molecule opiate antagonist became available for study – naltrexone [23]. Naltrexone took over as the preferred approach to opiate blocking due to its excellent efficacy, lack of medical safety issues at usual dosages, and specificity for opiates while maintaining broad generality across all different types of synthetic opiates. This lack of generality was, and continues to be, a particular problem for the antibodies because prescription opiate abusers used many classes of opiates, not just morphine or heroin. The antibodies produced against morphine or heroin were highly specific and did not block hydrocodone, codeine, fentanyl, methadone, buprenorphine and several other major classes of opiates that could be abused and dangerous. Up to six different vaccines would be needed to block all of these different opiate compounds, which was an unrealistically large target for any commercial medication development effort. Nevertheless, progress was made with vaccines to other drugs and in understanding how these vaccines and their resulting antibodies might work in the body to prevent euphoria and subsequent addiction or re-addiction.

COCAINE VACCINE

The cocaine vaccine is a cocaine hapten conjugated to inactivated cholera toxin B and called TA-CD. The TA-CD vaccine induces cocaine-specific antibodies that minimally bind to inactive cocaine metabolites such as benzoylecgonine, ecgonine methylester, and benzoic

acid. Thus, antibody-bound cocaine molecules are then broken down by pseudocholinesterase in the circulation, or by nonenzymatic hydrolysis which converts cocaine into inactive metabolites that no longer bind to the antibody and are subsequently excreted [24]. Because the metabolites do not bind antibody, this frees up the antibody to bind more cocaine and thereby prolong and potentiate its capacity for blocking more cocaine from entering the brain and leading to addiction and toxicity.

In the phase I trial (N = 34), TA-CD induced cocaine-specific antibodies in all vaccinated subjects. While these phase I subjects were in a drug-free residential program without access to cocaine, cocaine-dependent, actively vaccinated participants in subsequent outpatient and human laboratory studies reported attenuation in their subjective experience and euphoria from smoked cocaine [17, 20]. The antibody levels did not persist beyond one year, and the immunological blockade appeared to last approximately 2 to 4 months following the final vaccination, as corroborated by a decline in the level of circulating antibody levels during that time span.

Overall, the safety profile for the vaccine was quite favorable. Almost all recipients (33 of 34) reported local pain and/or tenderness at the injection site, with no difference between experimental and placebo groups or across the three different vaccine doses. Treatment-related systemic adverse effects that occurred in all groups included mild tachycardia, elevated temperature, and hypertension [19]. However, we had no serious adverse effects during vaccination or the 12 months of follow-up [17].

In the phase IIa trial (N = 18), TA-CD was administered at two dose levels ($100\text{ }\mu\text{g} \times 4$ injections, or $400\text{ }\mu\text{g} \times 5$ injections). The vaccine again elicited an immunological response from both the low- and high-dose groups. 7 Subjects from both groups developed cocaine-specific antibodies that persisted for at least 6 months. 10 Mean antibody levels were higher in the high-dose group. The high-dose group was also more likely to remain abstinent at 6-month follow-up (89% of the low-dose group experienced a relapse versus 43% of the high-dose group). Sixteen of 18 subjects (89%) successfully completed the study; there were no hospitalizations, deaths, or serious adverse effects [17]. The two subjects who did not complete the study received only one vaccination and did not report any adverse effects before discontinuing treatment.

In the initial phase IIb trial (N = 115), TA-CD was administered to cocaine-dependent, methadone-maintained subjects at a single dose level ($360\text{ }\mu\text{g} \times 5$ injections) in comparison to placebo. Subjects who received the vaccine were analyzed according to their antibody response and stratified into high- and low-antibody producing groups. The cutoff antibody level of above $20\text{ }\mu\text{g/ml}$ was determined from the previous studies as needed in order for the TA-CD vaccine to substantially decrease the intoxicating effects of a single smoked cocaine dose [20]. About one-third of the vaccinated subjects did not attain this peak antibody level, and about one-third attained levels above $43\text{ }\mu\text{g/ml}$. This higher level was calculated to be a sufficient dose to block most expected doses that cocaine addicts might take in order to try to override the antibody blockade. This high-antibody group showed a greater percentage of cocaine-free urines than any of the other groups: low antibody ($20\text{--}43\text{ }\mu\text{g/ml}$), no effective antibody (below $20\text{ }\mu\text{g/ml}$) or placebo [18]. The high antibody levels remained elevated at the 25 week follow-up, three months after the last vaccination. The safety profile of the vaccine was favorable with no significant adverse effects related to the vaccine.

The polyclonal antibody response to cholera toxin b produced substantial antibody responses to the cholera protein in every patient, but the reasons are unknown for producing lower levels of anti-cocaine antibodies in as many as one-third of these patients. This poor response is being actively investigated with a variety of very interesting leads related to

human genetics and the production of immunological tolerance for particular substances. In some patients, immunological recognition of cocaine before vaccination, as reflected in the presence of IgM antibodies capable of binding the drug, appears to be associated with this low level response. This could represent a T cell-independent response to cocaine, perhaps due to adduct formation by the drug to native proteins *in vivo* [24] that results in inhibition of the desired T cell-dependent response to the conjugate vaccine [25].

The antibody levels appear to decline substantially over about 3 months after the peak antibody response such that the patients who produced sufficient cocaine antibody levels for therapeutic efficacy in the initial response will no longer have sufficiently high levels to be therapeutic. A booster vaccination is needed to re-stimulate a rise in the antibody levels to their peak. Rather than needing the full series of five vaccinations again, however, a single vaccination may be sufficient to elevate antibody levels back to their therapeutic levels for an additional 3 months. Thus, if this pattern can be maintained, patients may need to get about six additional boosters given as one every 3 months for a period of protection lasting two years. Exposure to cocaine alone will not provoke an increase in antibodies because the cocaine molecule is too small to activate memory B cells by cross linking the antibodies expressed on their surface. However, after boosting with the conjugate vaccine, sufficient quantities of newly produced antibodies will be available to rapidly bind most of a usual dose of cocaine when it enters the bloodstream. This binding in circulation prevents the cocaine from rapidly leaving the blood vessels and entering the brain, heart or other organs, reducing the drug's euphoric effects. Because the antibody–cocaine complex is too large to pass thorough the blood-brain barrier in its normal state, the cocaine is then metabolized in the blood and liver to inactive metabolites by one of 3 mechanisms: spontaneous hydrolysis, tissue esterases (especially in the liver), or pseudocholinesterase (in the bloodstream) [26]. As discussed above, these metabolites are sufficiently different in structure that they do not bind to the cocaine antibodies, and are simply excreted from the body.

All of these Phase I and II cocaine vaccine studies succeeded due to a combination of first, a good antibody response from conjugation of cocaine with the cholera toxin carrier and second, the special advantage of the spontaneous and enzymatic hydrolysis of cocaine into inactive metabolites. For other abused drugs such as nicotine, morphine, or methamphetamine, this type of rapid metabolism to inactive derivative structures does not exist in the blood stream. Moreover, morphine and methamphetamine also have metabolic products (6-glucuronyl morphine and amphetamine, respectively) that retain significant pharmacological activity. When these other drugs are bound by antibodies, the substance is slowly metabolized in the liver or other tissue sites, or excreted unchanged [27]. As a result, these other drugs circulate in the bloodstream much longer when bound by antibody.

The cocaine vaccine is primarily for patients who can temporarily abstain from cocaine use for perhaps several weeks, but need additional therapeutic help with maintaining that abstinence. One pharmacological component to breaking that abstinence and relapsing to drug abuse is called the “priming effect”, which is related to craving and occurs across addictions [28]. Briefly, priming involves exposure to even a single small dose of cocaine (or any other abused drug) after a period of abstinence. This small exposure can markedly intensify craving, rather than reducing craving, and increases the risk for falling into a binge pattern of abuse and relapse. However, in the phase IIb cocaine trials the vaccine appeared to be effective even for subjects who did not abstain at all, but continued high level cocaine use. While they clearly did not benefit from having a diminished “priming effect,” they did appear to be blocked from cocaine euphoric effects and could not economically afford to override the antibody blockade [18]. Therefore, high antibody responders to vaccination may have complete blunting of deliberate attempts to override the vaccine's blockade by using more than an initial one or two drug doses. This high density of blockade by the

vaccine was not expected, and we are looking for potential replication of this finding among some subjects in the ongoing multi-site study of TA-CD.

The behavioral challenges for any successful vaccination program start with the need to have 2 to 3 months where the patient can be brought to a treatment site for five vaccinations. During these 2 to 3 months, the patients could be vulnerable to relapse if they have already discontinued drug use. While continued drug abuse during the 3 months of vaccination does not interfere with the vaccine's ability to stimulate the required antibody production, the patient does need to get these vaccinations at appropriate times over the 3 months (e.g., 2, 4, 8 and 12 weeks after the initial vaccination) and continued drug abuse may increase the risk of failure to appear for these follow-up visits. Thus, counseling or other treatment efforts will be critical to insure compliance with the schedule of vaccinations; such interventions could vary from residential substance abuse care to outpatient contingency management, in which patients are paid to come for the vaccinations with an escalating pay schedule for each vaccination obtained.

In summary, the success of the first placebo-controlled clinical trial of a cocaine vaccine [18] as well as the relative ease with which these vaccines can be manufactured, has encouraged cocaine vaccine development to move forward in an ongoing multi-site, phase IIb clinical trial. This four-month, double-blind, randomized, placebo-controlled, multi-center study will compare the effect of the cocaine vaccine to placebo in reducing cocaine use in 300 treatment-seeking, cocaine-dependent individuals. Patients receive five vaccinations over a period of twelve weeks and some subjects will likely attain therapeutic antibody levels from the vaccine in weeks 6–8 after the first three vaccinations. This phase IIb clinical test has a target date of June 2012 for completion of the last subject. Top line data analyses should be available by the end of 2012. Based on the success of this vaccine in the earlier clinical trials, this cocaine vaccine may be one of the first anti-addiction vaccines.

CONCLUSION

Antidrug vaccines represent an exciting development in the pharmacotherapy of chemical dependency. In addition to the clinical trials being conducted on vaccines for cocaine and nicotine dependence, preclinical development of vaccines for methamphetamine and heroin are ongoing. Future directions for vaccine trials will be moving toward new non-protein carriers that would have greatly simplified manufacturing and the use of more potent adjuvants than alum. Several outstanding adjuvants are commercially available, but not generally being licensed for anti-addiction vaccines. The nicotine vaccines are the most likely to first benefit from these new adjuvants due to the already ongoing interest of major pharmaceutical companies such as Novartis and GSK in these vaccines. Another likely focus will be on using booster injections with potentially different adjuvants from the original vaccine using alum in order to prolong antibody effects. Some work is also expected outside of the United States, in China in particular, for development and commercialization of these vaccines. Chinese companies have the capital needed, as well as the required government support, for moving these vaccines rapidly into the public health sectors where they are most needed.

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ABBREVIATIONS

SUD Substance use disorders

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