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Can you vaccinate against substance abuse?

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Abstract

Vaccines are being developed against substance abuse and most progress has been made with anti-cocaine, nicotine and opiate vaccines, but new ones are being developed for methamphetamine and may be in humans within 18 – 24 months. These haptenated vaccines share a common problem in that only about one-third of those vaccinated get a sufficiently robust antibody titer to enable them to effectively block drug use. This problem is being addressed with better carrier proteins and new adjuvants beyond alum. This review provides details about these developing vaccines that act through pharmacokinetic rather than pharmacodynamics blockade. Due to this pharmacokinetic mechanism of keeping abused drugs in the bloodstream and not allowing them entry into the brain or other organs, these vaccines have very few side effects compared to other blockers used in addictions treatment.

Keywords

clinical trials; cocaine; methamphetamine; vaccine

Introduction

Substance abuse is a serious health problem world-wide with a very limited number of effective pharmacological treatments, but some very interesting biologicals such as vaccines are being developed [1]. These vaccines act as blockers and can theoretically be developed against any abused drug except alcohol, because alcohol is too small and ubiquitous a molecule in the human body to generate an immune response even as a hapten linked to an immunogenic carrier protein [2]. This mechanism whereby a small non-immunogenic molecule, which all drugs of abuse are, can be chemically linked to an immunogenic carrier protein such as tetanus toxoid or cholera B subunit protein is critical to the manufacture of these vaccines and will be reviewed in more detail below. As blockers, these vaccines act indirectly and pharmacokinetically in a two-step process, rather than pharmacodynamically, in contrast to most anti-addiction blockers like naltrexone for opiates [2,3]. First, the

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vaccines provoke the production of antibodies against the abused drug after a series of vaccinations over 2 – 3 months and second, these antibodies bind to the abused drug and prevent it from leaving the blood stream and entering the brain, heart and other organs [4]. The rationale for developing these vaccine treatments involves several factors including the lack of any approved pharmacotherapies for the stimulants cocaine and methamphetamine. Furthermore, while existing treatments show some therapeutic success, relapse rates remain high even with these approved pharmacological treatments such as for opiates [5]. Other limitations to the use of currently approved therapies include high cost, limited availability, problems with compliance, and, diversion in the case of opiate agonists, such as methadone [4,6–8].

Vaccines have the great strength of being highly specific for the abused drug and not having significant interactions with neurotransmitters or hormones. However, this specificity also has limitations. For example, vaccines against heroin must also block two active metabolites of heroin that are readily produced by serum and liver esterases: 6-acetylmorphine (6-AM) and morphine [9]. Because 6-AM is considered to cause the immediate euphoric effects of heroin administration [9], a vaccine that can produce antibodies to heroin, morphine and 6-AM is essential for clinical efficacy. Similarly, methamphetamine's major metabolite is amphetamine so that an effective vaccine must produce antibodies that cross-react with amphetamine [10]. However, the inactive metabolites for both heroin and methamphetamine must not significantly interact with the antibodies produced by the respective vaccines or the antibody will be rapidly occupied fully with inactive metabolites, and its blockade be readily overcome by simply using the abused drug repeatedly over a relatively brief period of time. Thus, designing the chemical linkage between the abused drug or hapten and the carrier protein is critical to insure the desired cross-reactivity while maintaining minimal binding of the inactive metabolites with the antibody. Over the past 20 years significant success has been achieved in developing these hapten to protein linkages in order to attain this balance of specificity and cross-reactivity [4].

2. Development of anti-addiction vaccines and their mechanism of action

Briefly reviewing the development of drug addiction vaccines against nicotine, cocaine, methamphetamine and opiates is important to understanding the different approach for these blockers compared to other pharmacodynamic antagonists. The existing treatment agents target neurotransmitter effector systems in the brain such as opioid, dopaminergic or nicotinic cholinergic systems through pharmacodynamic mechanisms, but vaccines act as 'pharmacokinetic' antagonists. Since the vaccine stimulates the production of drug-specific antibodies that can bind to the drug in the circulating blood and extracellular fluid, this action should reduce or slow the distribution of the drug to brain and attenuate the drug's reinforcing effects. These concepts are based on the greater reinforcing strengths of drugs when administered with shorter injection or infusion times [11–13]. For example, rhesus monkeys selfadminister more cocaine intravenously if the infusion rate is increased even though the dose is held constant [11]. Human drug users report greater effects of morphine (e.g., 'High'; 'Drug effect') with faster IV infusion rates [13]. The reduction in drug reward and the attenuation of self-administration reported in the many animal studies support these vaccines' slowing the entry rate of the drug into the brain more than simply holding the drug

completely out of the brain. Indeed, nicotine, cocaine, methamphetamine and morphine levels were significantly decreased in brains, and blood levels were higher of appropriately vaccinated rats [14].

Vaccination against addictions requires a protein–hapten combination such that the hapten, which is the abused drug, is covalently linked to the carrier protein, which provides the immunological entity for producing a high affinity, immunoglobulin G type (IgG) [2]. This process is not uniform across individual patients, however, and up to one-third of patients do not produce a significant antibody response to vaccination. The explanation for this lack of a robust immune response remains unknown, but one contributor to this lack of response for opiate and cocaine vaccines appears to be a peculiar immunological reaction that develops low affinity immunoglobulins spontaneously in some humans and in animal models from prolong exposure to the abused morphine or cocaine, respectively [15,16]. This ‘auto-immunization’ is an altered immune state with circulating IgM, which has a low affinity for morphine or cocaine, respectively, and does not provide any effective blockade to morphine’s or cocaine’s effects on the body such as euphoria [15,16]. More critically this IgM appears to be a marker of immune tolerance or suppression of an IgG response to these anti-addiction vaccines [17]. This IgM marker has so far only been demonstrated in humans given a cocaine vaccine and not in to nicotine in smokers, but in principle individuals with chronic exposure to opiates and possibly methamphetamine and other haptenated vaccines may develop this ‘auto-immunization’ and immune tolerance to subsequent vaccination. Hypothetically, the drug such as morphine or cocaine is chemically combining with normal human proteins, as has been described about 15-years ago for morphine and in 2002 for cocaine [16,18]. Toki and Yamano found morphine 6-dehydrogenase, which catalyzes the dehydrogenation of the 6-hydroxy group of morphine to produce morphinone in the liver. It was also found that morphinone antagonizes morphine analgesia and binds with serum proteins to form a potential anti-morphine vaccine and associated low affinity antibodies. Similar low affinity anti-cocaine antibodies can be produced with prolonged high-dose cocaine exposure [16]. These low affinity antibodies appear to contribute to morphine tolerance, but more importantly for our antiaddiction vaccine strategy, these antibodies are markers of suppression of high affinity IgG being produced in response to an anti-morphine or anti-cocaine vaccine. The extent of these IgM markers in humans appears to be up to 80% of heroin addicts and 20% of cocaine patients [16,17,19], thereby presenting a significant potential challenge to making effective vaccines in humans.

With no FDA approved treatments for cocaine or methamphetamine dependence, these two abused drugs have the fewest regulatory hurdles to getting approval as a safe and efficacious treatment. The other two abused drugs with vaccines in the pipeline include nicotine and opiates. Both nicotine and opiate vaccines face the hurdles of other FDA approved treatments such as nicotine replacement, bupropion and varenicline for nicotine and methadone, buprenorphine and naltrexone for opiates [3,20]. The most direct competitive hurdle would be for an opiate vaccine to show greater efficacy than naltrexone, since they are both blocking agents. The liver toxicity black box warning on naltrexone might offer a safety advantage to an opiate vaccine, however. Opiate addiction vaccines have an additional challenge that is not faced with other drugs of abuse, because the current epidemic of prescription opiate abuse involves at least five different chemical entities and

each of them will require a separately developed vaccine. These entities include morphine, codeine, thebain (hydrocodone, oxycodone), methadone and buprenorphine, which have distinct chemical structures and require separately developed vaccines.

3. Specific vaccines by abused drug

The history of anti-addiction vaccines begins 40 years ago with a vaccine directed at morphine and was followed by cocaine and nicotine vaccines in the early 1990's and most recently a methamphetamine vaccine (although a methamphetamine monoclonal antibody has been under development since the 1990's and recently had its first trial in humans) [21–23]. The first vaccine conjugated a morphine hapten to bovine serum albumen (BSA) through a 6-succinylmorphine (6SM) linkage to lysine residues on BSA. Other studies showed that binding specificity differed depending on the hapten used [24–26]. Other examples of vaccines for opiates include a bivalent morphine--heroin vaccine developed using tetanus toxoid as the carrier protein, which prevented rats from acquiring heroin self-administration [27,28]. Another study used a hapten structure where the linker was attached to the nitrogen of nor-heroin. This vaccine reduced heroin-induced anti-nociception and acquisition of heroin self-administration [29]. However, rats administered a similar vaccine that was based on nor-morphine did not block heroin self-administration, due to a lack of affinity for 6-AM [29]. In addition, Stowe found that their nor-morphine vaccine was unable to block the anti-nociceptive effect of oxycodone, as might be expected based on the differing chemical structures of morphine and oxycodone. In spite of these successful animal studies of opiate vaccines, no studies have been undertaken in humans after the successful introduction of methadone and naltrexone as clinically effective agonist and antagonist approaches to opiate dependence in humans. Furthermore, the recent successes of buprenorphine and depot naltrexone (Vivitrol) have reinforced this pharmacological approach to treatment [3]. The role of a heroin or morphine vaccine, therefore, seems more circumscribed to countries or cultures where methadone substitution approaches and/or naltrexone approaches have failed to be effective for various reasons.

The cocaine vaccines have had a similar number of successful animal studies with various carrier proteins and linker strategies, but only one vaccine, TA-CD using a cholera B subunit carrier protein has gone into clinical trials [2,30,31]. The Phase I and initial Phase II studies showed no significant safety concerns at doses up to 1000 μg, and good antibody production following up to five vaccinations at a dose of 400 μg [32,33]. A placebo controlled randomized clinical trial of this vaccine showed significant efficacy compared to placebo, and a wide range in antibody response with those having higher antibody levels showing significantly more cocaine-free urines from the antibody induced blockade of cocaine effects, as previously shown by Haney *et al*. [34]. Recently a national, multisite clinical trial of this vaccine was completed with preliminary results expected in late 2013.

The methamphetamine vaccine is still in pre-clinical development using a tetanus toxoid carrier linked through a succinyl group to the methamphetamine and combined with a new, phospholipid adjuvant from Eisai, which targets the toll 4 receptor [35]. The preliminary results are very promising based on both antibody production and behavioral assays of conditioned place preference and locomotor activity in response to methamphetamine,

which are both attenuated by this vaccine [36]. FDA approval to go into Phase I clinical trials is expected within the next 18 months.

The nicotine vaccines are the only ones that have gone into full commercial development with large pharmaceutical companies (GSK, Middlesex, UK and Novartis, Basel, Switzerland). The preliminary studies with these vaccines were quite promising for the one-third to 50% of patients who got a substantial antibody response to the vaccine [37]. Those patients with high antibody levels had a better clinical outcome of remaining abstinent from smoking. However, subsequent larger scale clinical trials failed to meet the Phase III benchmark outcomes for sustained abstinence from smoking, and clinical development of these vaccines in both companies appears to be on hold pending potential use of stronger adjuvants than the alum used in these initial vaccine studies. Such adjuvants would be expected to improve the antibody response in making more individuals produce antibodies and making those antibody levels both higher and more sustained beyond the 2 -- 3 months that these antibodies remain at blocking levels with current vaccines.

4. Expert opinion

In summary, we have the capacity to therapeutically vaccinate against substance abuse, and these vaccines hold promise as a measure to prevent relapse to substance abuse in abstinent patients. However, these vaccines will clearly not work in every substance abuser for a wide variety of reasons. First, perhaps one-quarter of substance dependent patients appear to have a poor antibody response to existing vaccines. This problem may be addressed with more potent adjuvants such as the phospholipid adjuvants. One particular challenge appears to be those opiate and cocaine abusers who have already ‘auto-vaccinated’ themselves and produced an immunological suppression of high affinity IgG producing cells and instead produce a low affinity IgM [17]. However, immune complex diseases do not occur due to the small size of the hapten, which prevents cross-linking of these antibodies. Second, the initial period of vaccination requires about 3 months of cooperation and returning for four to five vaccinations over that period, which many substance abusers would find difficult to sustain. Third, other effective pharmacological treatments exist for opiates and nicotine, and while a blocker medication such as a vaccine might have a unique role for nicotine dependence, opiates already have a blocker in depot naltrexone that has greater breath of coverage than a vaccine and can last almost as long after a single administration as does a vaccine given repeatedly. Fourth, these vaccines are not the typical preventative measures, for which vaccines are usually considered. There seems relatively little role for large scale vaccination using them in order to prevent or even delay the onset of drug abuse. Even as relatively long acting agents, injections would most likely be needed every 2 – 3 months, and use of the drug does not boost the antibody response that way exposure to an infectious agent boosts the antibody response with a typical preventative vaccine. Nevertheless, human clinical trials for vaccines against cocaine and nicotine addiction have shown promising results and support the vaccine approach to addiction treatment [31,37].

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Bibliography

1. United Nations Office on Drugs and Crime: UNODC. World Drug Report 2010 (United Nations Publication, Sales No. E.10.XI.13). Available from: http:/www.unodc.org/documents/wdr/WDR_2010/World_Drug_Report_2010_lo-res.pdf.
2. Shen XY, Orson FM, Kosten TR. Vaccines against drug abuse. Clin Pharmacol Ther. 2012; 91(1): 60–70. [PubMed: 22130115]
3. Stotts AL, Dodrill CL, Kosten TR. Opioid dependence treatment: options in pharmacotherapy. Expert Opin Pharmacother. 2009; 10(11):1727–1740. [PubMed: 19538000]
4. Orson FM, Kinsey BM, Singh RA, et al. The future of vaccines in the management of addictive disorders. Curr Psychiatry Rep. 2007; 9(5):381–387. [PubMed: 17915077]
5. Veilleux JC, Colvin PJ, Anderson J, et al. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev. 2010; 30(2):155–166. [PubMed: 19926374]
6. Kahan M, Srivastava A, Ordean A, Cirone S. Buprenorphine: new treatment of opioid addiction in primary care. Can Fam Physician. 2011; 57(3):281–289. [PubMed: 21402963]
7. Kreek MJ, Borg L, Ducat E, Ray B. Pharmacotherapy in the treatment of addiction: methadone. J Addict Dis. 2010; 29(2):200–216. [PubMed: 20407977]
8. Obadia Y, Perrin V, Feroni I, et al. Injecting misuse of buprenorphine among French drug users. Addiction. 2001; 96(2):267–272. [PubMed: 11182872]
9. Inturrisi CE, Schultz M, Shin S, et al. Evidence from opiate binding studies that heroin acts through its metabolites. Life Sci. 1983; 33(Suppl 1):773–776. [PubMed: 6319928]
10. Kosten, TR.; Newton, TF.; De La Garza, R., II; Haile, CN. Cocaine and methamphetamine dependence: advances in treatment. Arlington, VA: APPI Press; 2012. ISBN-10: 1585624071
11. Woolverton WL, Wang Z. Relationship between injection duration, transporter occupancy and reinforcing strength of cocaine. Eur J Pharmacol. 2004; 486:251–257. [PubMed: 14985046]
12. De Wit H, Bodker B, Ambre J. Rate of increase of plasman drug level influences subjective response in humans. Psychopharmacology (Berl). 1992; 107:352–358. [PubMed: 1615136]
13. Marsch LA, Bickel WK, Badger GJ, et al. Effects of infusion rate of intravenously administered morphine on physiology, psychomotor, and self-reported measures in humans. J Pharmacol Exp Ther. 2001; 299:1056–1065. [PubMed: 11714895]
14. Shen, X.; Kinsey, B.; Lopez, Y., et al. Evaluation of peptide and conjugate morphine vaccines in mice. College on Problems of Drug Dependence; 74th Annual Meeting; Palm Springs, CA. 2012. Poster Session
15. Ringle DA, Herndon BL. Immunologic effects of morphine administration in rabbits. J Immunol. 1975; 115:876–883. [PubMed: 50375]
16. Deng SX, Bharat N, Fishman MC, Landry DW. Covalent modification of proteins by cocaine. Proc Natl Acad Sci. 2002; 99:3412–3416. [PubMed: 11891282]
17. Orson FM, Rossen RD, Shen XY, et al. Spontaneous development of IgM anti-cocaine antibodies in habitual cocaine users: effect on IgG antibody responses to cocaine - cholera toxin b conjugate vaccine. Amer J Addiction. 2013; 22(2):169–174.
18. Toki S, Yamano S. Production of morphinone as a metabolite of morphine and its physiological role. Yakugaku Zasshi. 1999; 119(4):249–267. [PubMed: 10228449]
19. Biagini RE, Klincewicz SL, Henningsen GM, et al. Antibodies to morphine in workers exposed to opiates at a narcotics manufacturing facility and evidence for similar antibodies in heroin abusers. Life Sci. 1990; 47:897–908. [PubMed: 2215072]

20. Dani, JA.; Kosten, TR.; Benowitz, N. Nicotine and tobacco: pharmacology. In: Ries, RK.; Fiellin, DA.; Miller, S.; Saitz, R., editors. Principles of addiction medicine. 4th edition. Philadelphia, PA: Kosten Pharmacology editor Lippincott Williams & Wilkins; 2009. ISBN-10: 0-7817-7477-2
21. Berkowitz B, Spector S. Evidence for active immunity to morphine in mice. Science. 1972; 178(67):1290–1292. [PubMed: 4640066]
22. Bonese KF, Wainer BH, Fitch FW, et al. Changes in heroin self-administration by a rhesus monkey after morphine immunization. Nature. 1974; 252(5485):708–710. [PubMed: 4474602]
23. Gentry WB, Ruedi-Bettschen D, Owens SM. Development of active and passive human vaccines to treat methamphetamine addiction. Hum Vaccin. 2009; 5(4):206–213. [PubMed: 19276653]
24. Van Vunakis H, Wasserman E, Levine L. Specificities of antibodies to morphine. J Pharmacol Exp Ther. 1972; 180(2):514–521. [PubMed: 5062300]
25. Wainer BH, Fitch FW, Fried J, Rothberg RM. A measurement of the specificities of antibodies to morphine-6-succinyl-BSA by competitive inhibition of 14 C-morphine binding. J Immunol. 1973; 110(3):667–673. [PubMed: 4688917]
26. Koida M, Takahashi M, Muraoka S, Kaneto H. Antibodies to BSA conjugates of morphine derivatives: strict dependency of the immunological specificity on the hapten structure. Jpn J Pharmacol. 1974; 24(1):165–167. [PubMed: 4134640]
27. Anton B, Leff P. A novel bivalent morphine/heroin vaccine that prevents relapse to heroin addiction in rodents. Vaccine. 2006; 24(16):3232–3240. [PubMed: 16494974]
28. Anton B, Salazar A, Flores A, et al. Vaccines against morphine/heroin and its use as effective medication for preventing relapse to opiate addictive behaviors. Hum Vaccin. 2009; 5(4):214–229. [PubMed: 19242094]
29. Stowe GN, Vendruscolo LF, Edwards S, et al. A vaccine strategy that induces protective immunity against heroin. J Med Chem. 2011; 54(14):5195–5204. [PubMed: 21692508]
30. Bagasra O, Forman LJ, Howeedy A, Whittle P. A potential vaccine for cocaine. Immunopharmacology. 1992; 23:173–179. [PubMed: 1500284]
31. Martell BA, Orson FM, Poling J, et al. Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: a randomized, double-blind, placebo-controlled efficacy trial. ArchGen Psychiatry. 2009; 66:1116–1123.
32. Kosten TR, Rosen M, Bond J, et al. Human therapeutic cocaine vaccine: safety and immunogenicity. Vaccine. 2002; 20:1196–1204. [PubMed: 11803082]
33. Martell BA, Mitchell E, Poling J, et al. Vaccine pharmacotherapy for the treatment of cocaine dependence. Biol Psychiatry. 2005; 58:158–164. [PubMed: 16038686]
34. Haney M, Gunderson EW, Jiang H, et al. Cocaine-specific antibodies blunt the subjective effects of smoked cocaine in humans. Biol Psychiatry. 2010; 67(1):59–65. [PubMed: 19846066]
35. Ishizaka ST, Hawkins LD. E6020: a synthetic toll-like receptor 4 agonist as a vaccine adjuvant. Expert Rev Vaccines. 2007; 6(5):773–784. [PubMed: 17931157]
36. Shen XY, Kosten TA, Lopez AY, et al. A vaccine against methamphetamine attenuates its behavioral effects in mice. Drug Alcohol Dependence. 2012; 129(1–2):41–8. [PubMed: 23022610]
37. Hatsukami DK, Jorenby DE, Gonzales D, et al. Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. Clin Pharmacol Ther. 2011; 89:392–399. [PubMed: 21270788]