LEADING ARTICLE

Drugs 2003; 63 (4): 341-352
0012-6667/03/0004-0341/$33.00/0

Vaccines Against Drugs of Abuse
A Viable Treatment Option?

Kathleen M. Kantak

Laboratory of Behavioral Neuroscience, Department of Psychology, Boston University, Boston, Massachusetts, USA

Abstract

Drug addiction is a chronically relapsing brain disorder. There is an urgent need for new treatment options for this disease because the relapse rate among drug abusers seeking treatment is quite high. During the past decade, many groups have explored the feasibility of using vaccines directed against drugs of abuse as a means of eliminating illicit drug use as well as drug overdose and neurotoxicity.

Vaccines work by inducing drug-specific antibodies in the bloodstream that bind to the drug of abuse and prevent its entry into the brain. The majority of work in this area has been conducted with vaccines and antibodies directed against cocaine and nicotine. On the basis of preclinical work, vaccines for cocaine and nicotine are now in clinical trials because they can offer long-term protection with minimal treatment compliance. In addition, vaccines and antibodies for phencyclidine, methamphetamine and heroin abuse are currently under development. An underlying theme in this research is the need for high concentrations of circulating drug-specific antibodies to reduce drug-seeking and drug-taking behaviour when the drug is repeatedly available, especially in high doses.

Although vaccines against drugs of abuse may become a viable treatment option, there are several drawbacks that need to be considered. These include: (i) a lack of protection against a structurally dissimilar drug that produces the same effects as the drug of choice; (ii) a lack of an effect on drug craving that predisposes an addict to relapse; and (iii) tremendous individual variability in antibody formation. Forced or coerced vaccination is not likely to work from a scientific perspective, and also carries serious legal and ethical concerns.

All things considered, vaccination against a drug of abuse is likely to work best with individuals who are highly motivated to quit using drugs altogether and as part of a comprehensive treatment programme. As such, the medical treatment of drug abuse will not be radically different from treatment of other chronic diseases.

Vaccination as an approach for treating drug addiction is not a recent development. Its feasibility was demonstrated nearly 30 years ago. The first published report described the synthesis of a morphine hemisuccinyl-bovine serum albumin conjugate having equal affinity for morphine and heroin.[1] After immunising a single rhesus monkey trained to self-administer both heroin and cocaine, heroin self-administration selectively extinguished. It took an approximately 16-fold increase in heroin dose for the monkey to reinitiate drug-taking behaviour. Although these results were encouraging, the heroin vaccine was never developed for human use, at least in part because other neuro-

pharmacological approaches that blocked abstinence symptoms (methadone) or prevented relapse (naltrexone) appeared to be more promising at the time.

The impetus for the development of vaccines to treat drug addiction stems from the work of Owens and colleagues who led the way in the 1980s by developing monoclonal antibodies to treat drug overdose. It was not until the early 1990s that interest in developing vaccines for treating drug addiction was renewed. Early studies targeted cocaine because its addiction lacked effective pharmacotherapies.[2] By the end of the decade, vaccines and antibody approaches emerged not only for potentially treating cocaine addiction, but also addictions to nicotine, phencyclidine and methamphetamine. Given the success of some drug vaccines in reaching clinical trials (see following sections), development of a heroin vaccine is currently being revisited.[3]

The important question is, are vaccines a viable treatment option for drug addiction? A review of the relevant research literature suggests that drug-specific vaccines, as part of a comprehensive programme, may be useful in the treatment of this complex brain disease.

1. Cocaine

1.1 Catalytic Antibodies

The headline on an accompanying article reads, 'Enzyme May Blunt Cocaine's Action'.[4] The 'enzyme' refers to a catalytic monoclonal antibody that binds cocaine, and subsequently hydrolyses the alkaloid into the inactive products ecognine methyl ester and benzoic acid.[5] The unique feature of this preparation is that after the hydrolysis of cocaine and release of metabolites, the antibody becomes free for further enzymatic activity. Through this mechanism, it was anticipated that serum cocaine concentrations could decrease to the point where cocaine was no longer reinforcing and thus its use would extinguish. The initial artificial enzymes, 3B9 and 6A12, lacked sufficient catalytic activity to be clinically useful, but 3 years later, Landry and colleagues generated a more potent catalytic monoclonal antibody (15A10) against cocaine.[6]

After passive administration of 15A10 to rats, *in vivo* analyses were carried out.[7] Following a lethal intravenous infusion of cocaine (16 mg/kg), 15A10 increased the survival rate. Five of five rats receiving 50 mg/kg 15A10 survived the lethal infusion, whereas four of five rats receiving 15 mg/kg 15A10 survived. Further testing ascertained that 15A10 afforded approximately 3-fold protection against the lethal and seizure-inducing effects of cocaine. In evaluating cocaine self-administration in which a moderate dose of cocaine (0.3 mg/kg/infusion) was repeatedly available, treatment with 9–12mg of 15A10 produced a pattern and amount of cocaine self-administration much like that produced by saline substitution.[7] Testing with the structurally dissimilar stimulant bupropion and with a non-drug milk reinforcer revealed that the reductions in cocaine self-administration after treatment with 15A10 were both pharmacologically and behaviourally specific for cocaine. All rats returned to pretreatment levels of responding within 48 hours of 15A10 treatment. Against a full range of intravenously self-administered cocaine doses (0.015–0.5 mg/kg/infusion), 30 and 100 mg/kg 15A10 blocked drug-taking behaviour up to the 0.125 mg/kg/infusion dose of cocaine.[8] The antagonism of self-administration of low to moderate doses of cocaine was evident 30 minutes after 15A10 treatment but persisted beyond this time only after treatment with 100 mg/kg of the antibody. By 72 hours, 15A10 was no longer effective against cocaine.

My opinion is that 15A10 may lack sufficient catalytic activity to be clinically useful because it does not protect against high doses of repeatedly self-administered cocaine. It is also clear that 15A10 is far from being optimised with respect to kinetic parameters to afford long-term protection. The effects of a murine catalytic monoclonal antibody would be short-lived and may therefore not be suitable for treating cocaine addiction, which requires long-term treatment. As suggested, these

drawbacks may be mitigated by the development of polyclonal catalytic antibodies[9] or humanised monoclonal catalytic antibodies[10] against cocaine.

1.2 Vaccines

Several groups have explored the possibility of active immunisation with cocaine-protein conjugates as a means for treating cocaine addiction. The notion that a vaccine against cocaine could be developed was first investigated a decade ago.[11] The approach taken by Bagasra and colleagues was based on the premise that cocaine cannot produce an immune response. However, if conjugated with an immunogenic carrier molecule, administration of the conjugate would induce the immune system to produce antibodies against cocaine. Using the carrier protein KLH (keyhole limpet haemocyanin), anti-cocaine antibodies were induced in rats and shown to reach serum levels ranging from 0.004 to 0.019 mg/ml.[11] In these rats, the analgesic effects of 25 mg/kg cocaine were reduced. Furthermore, levels of circulating antibody negatively correlated with the reaction time on the hotplate analgesia test. As none of the animals showed complete resistance to this single moderate dose of cocaine, it was suggested that the immunisation dose and regimen were not optimised. Nevertheless, this study prompted other investigators to explore this approach further.

Developed by Janda and colleagues, active immunisation with a novel cocaine-KLH conjugate, GNC-KLH, was shown to suppress locomotor activity and stereotyped behaviour induced by an injection of cocaine but not amphetamine.[12] A later study[13] indicated that antibody titres (quantity of antibodies in the blood) rose to over 25 000 in rats given three injections of GNC-KLH 250μg over a 5-week immunisation period. This level of antibody was sufficient to block reinstatement of responding induced by a cocaine prime (a single non-contingent injection of cocaine) but was less effective when a 3-fold increase in the cocaine-priming dose was available. When cocaine was freely available, cocaine-maintained responding rose to approximately 200% above baseline. These findings suggest that the effects of GNC-KLH are easily overcome, either by small increases in cocaine dose or by doubling the frequency of cocaine intake. The modest antagonism of the reinforcing effects of cocaine is probably the result of low titres of anti-cocaine antibodies induced by GNC-KLH.

These investigators subsequently developed a second-generation cocaine-KLH conjugate, GND-KLH. Immunisation (3 times 250μg over 5 weeks) with GND-KLH had a pronounced effect on suppressing the psychomotor stimulant effects of cocaine 15 mg/kg.[14] As this effect was sustained for up to 12 days after immunisation, GND-KLH was an improvement over GNC-KLH by offering longer-term protection against cocaine. However, anti-cocaine antibody titres remained in the 25 000 range, making it unlikely that GND-KLH would protect against high doses of repeatedly self-administered cocaine. Additional efforts to blunt the effects of cocaine with cocaine-KLH conjugates have met with limited success as well.[15,16]

Perhaps a more viable approach is the development of a cocaine vaccine that used a synthetic derivative of norcocaine conjugated to the immunogenic carrier protein bovine serum albumin.[17] In mice immunised with three tri-weekly 50μg injections of the vaccine IPC-1010 (ImmuLogic Pharmaceutical Corporation, Waltham, Massachusetts, USA, antibody titres could rise to over 100 000 by 3 weeks after the last boost and remained at these levels for up to 4 months. With periodic administration of a booster, antibody titres were maintained for more than a year. Using immune sera from mice with antibody titres >100 000, competition ELISA procedures demonstrated that increasing concentrations of cocaine, norcocaine (active metabolite) and cocaethylene (an active derivative produced when ethanol is consumed with cocaine) reduced the levels of unbound antibody in a concentration-dependent manner, thus demonstrating their ability to bind to the antibody. The inactive cocaine metabolites, ecgonine-methyl ester and benzoylecgonine, did not appreciably alter

the levels of unbound antibody with concentrations up to 5×10^{-3} mol/L and, thus, did not bind to the antibody. Furthermore, anti-cocaine antibodies did not recognise the structurally dissimilar local anaesthetics procaine and lidocaine. The cocaine binding capacity of anti-cocaine antibodies after active immunisation with IPC-1010 (8.5 μmol/L) exceeds the peak arterial plasma concentrations of cocaine reported in humans after repeated use of the drug (7.4 μmol/L).[18] After intravenous administration of cocaine, significant changes in the distribution of cocaine are observed in immunised animals that favour its therapeutic use (increase in plasma, decrease in brain and heart). The rate of removal of cocaine from the plasma was unaffected by the presence of the anti-cocaine antibodies. In addition, cocaine administration did not appear to influence antibody clearance. Thus, as cocaine metabolises and clears from the system, the antibody is available for further binding.[17]

To test the effect of IPC-1010, (now consisting of the norcocaine derivative coupled to the immunogenic protein rec cholera toxin B) rats were trained to self-administer cocaine 1 mg/kg, tested with various doses of cocaine, immunised with the vaccine (3 times 10μg over 6 weeks) and then tested again with various doses of cocaine.[19] Control animals were immunised with alum alone. Serum antibody levels ranged from 0.008 to 0.709 mg/ml (average 0.08 mg/ml) 2 weeks after the last vaccine injection. Preliminary tests with the anti-cocaine monoclonal antibody MO240 suggested that a minimum of 0.05 mg/ml cocaine-specific antibody in the serum was necessary for the cocaine vaccine to antagonise the effects of cocaine. Therefore, rats immunised with IPC-1010 were divided into subgroups of rats having serum antibody levels > and <0.05 mg/ml. Only rats having serum antibody levels >0.05 mg/ml displayed attenuated drug-seeking behaviour and drug infusions across the range of doses examined. The ascending limb of the inverted U-shaped dose-response curve was significantly shifted to the right for both drug-seeking behaviour and number of drug infusions earned, indicating that immunisation with the cocaine vaccine antagonised the reinforcing effects of cocaine in this subgroup of rats. An analysis of total drug intake for the entire session (number of drug infusions earned × available dose) revealed that for doses up to 3.0 mg/kg, rats with antibody levels >0.05 mg/ml consumed less cocaine overall at each dose available after immunisation compared with before immunisation. Drug-seeking behaviour remained at low levels and was never restored to pre-immunisation levels.[19] Moreover, with unit infusion doses of cocaine 5.6 and 10 mg/kg, intakes that would have been high enough to produce convulsions and even death in non-immunised animals produced only mild stereotypic motor movements in immunised animals and were associated with low levels of drug-seeking behaviour. These data indicate that some minimum threshold concentration of circulating anti-cocaine antibody is necessary to observe reductions in the seeking and taking of a normal cocaine dose. Furthermore, there was no evidence that even 10-fold increases in the normal cocaine dose would surmount the protective effects of the antibody for blunting the reinforcing effects of cocaine.

Additional studies determined that daily exposure to cocaine during the 6-week immunisation period did not influence the ability of the vaccine to induce anti-cocaine antibody formation or to block cocaine self-administration behaviour.[20] Furthermore, immunisation with IPC-1010 did not produce any significant changes in food-seeking behaviour or the number of food pellets earned, indicating that the ability of the vaccine to reduce cocaine self-administration behaviour is behaviourally specific and not a side effect of immunisation. On the basis of these pre-clinical findings, the norcocaine derivative-rec cholera toxin B conjugate was approved for clinical testing.

1.2.1 Clinical Trials

In a phase I clinical study, the safety and immunogenicity of this conjugate (currently designated TA-CD, Xenova Group plc, Berkshire, UK) were evaluated in three groups of abstinent cocaine abusers.[21] Three doses of the vaccine (13, 82 and 709μg) were examined, with each participant re-

ceiving three injections over a 2-month period. A placebo was examined in a separate group of participants. Blood samples were obtained at various times post-immunisation (up to 1 year). Patients were also monitored for signs of local and systemic adverse effects. Immunisation with TA-CD induced cocaine-specific antibodies in the three groups of participants. The first clearly detectable anti-cocaine antibodies appeared on day 28 (14 days after the second vaccination). This corresponded in time with the initial appearance of decreases in cocaine self-administration behaviour in rats.[20] The antibody response was maximal after the third vaccination and remained at this level for 4 months. As with rats, there was substantial individual-to-individual variability in the magnitude of the antibody response. The highest dose of TA-CD (709μg × 3) induced the highest antibody levels, which were more than 2-fold higher than levels produced by the two smaller doses of the vaccine. By 1-year post-immunisation, antibody levels in all three groups declined to baseline values. Adverse effects were minor and included small temperature elevations, mild pain and tenderness at the site of injection, and muscle twitch at the highest dose.

Although the results of the phase I study demonstrated that TA-CD was relatively 'safe' and could induce a significant anti-cocaine antibody response, equilibrium dialysis determined that a pool of serum from individuals immunised with the lowest vaccine dose (13μg) only contained an average of 0.003 mg/ml specific antibody. This level was almost 20-fold lower than the target level predicted to be necessary for antagonising the effects of cocaine over a range of typically used doses.[19,20] It was concluded that future studies with TA-CD needed to reconsider vaccination schedule and vaccine dose for producing an adequate level of anti-cocaine antibodies to protect against the effects of a wide range of cocaine doses.

Phase II clinical studies with TA-CD are currently underway but press releases describing preliminary findings are available on the World Wide Web.[22,23] In the initial phase II study, an improved dose administration regimen was initiated to boost anti-cocaine antibody levels. Four injections of 82μg each were administered at 0, 2, 4 and 8 weeks to nine outpatients. The vaccine produced high levels of antibodies against cocaine and approached levels produced in the rodent self-administration model. As in preclinical and previous clinical studies, significant levels of antibody were detected after the second vaccination. The levels peaked at 12 weeks and declined at further time points until 1 year. Anecdotally, five patients abstained from cocaine during the 12-week trial, while four who relapsed reported reductions in the usual effects of cocaine. In order to test for the efficacy of TA-CD in cocaine addicts, a phase IIb study is set to begin early in 2002 in which immunised individuals will receive challenge doses of cocaine and their behaviour monitored using quantitative measurements.

1.2.2 Anti-Idiotypic Cocaine Vaccine

The latest advance in cocaine vaccines would be the development of an anti-idiotypic cocaine vaccine. This approach uses an antibody molecule as the antigen, the configuration of which mimics the configuration of the cocaine molecule. In a feasibility study,[24] anti-cocaine monoclonal antibodies (Ab1) were first produced by active immunisation with a cocaine-protein conjugate. Antibodies identified as being anti-idiotypic (Ab2β) were linked to KLH and the new conjugate was used as a vaccine to induce the formation of antibodies to Ab2β. These antibodies would have anti-cocaine effects because of the structural similarities between cocaine and the antigen. This approach circumvents the problems associated with the instability of cocaine analogues linked to the carrier protein. Injection of the Ab2-KLH conjugate in mice reduced the level of cocaine in the brain following an intraperitoneal challenge injection of cocaine 5 mg/kg. However, critical preclinical behavioural and pharmacokinetic tests are yet to be conducted.

1.3 Therapeutic Potential

In terms of clinical treatment of cocaine addiction with a cocaine vaccine, it is likely to work best with individuals who are highly motivated to quit using drugs altogether since anti-cocaine antibodies are liable to have pharmacological specificity. A cocaine vaccine induces antibodies that are highly specific for recognising cocaine and its active metabolites, and therefore they would not recognise structurally dissimilar stimulants. As a result, a cocaine vaccine would not guard against relapse to the use of other stimulants by cocaine addicts, unless the motivation level to quit using drugs is high.[25]

An additional benefit of treating cocaine addicts with a cocaine vaccine relates to the recognition of cocaethylene by anti-cocaine antibodies induced by the vaccine. Cocaethylene is a potent stimulant formed in the liver when cocaine and ethanol are used together,[26] and is more toxic than either drug alone.[27,28] There is a strong relationship between ethanol consumption and cocaine relapse in cocaine dependent individuals seeking treatment,[29] making this potentially deadly drug combination an important target in cocaine addiction treatment. Cocaine and cocaethylene show identical binding curves in a competition ELISA that measures the specificity of anti-cocaine antibody binding,[17] suggesting that treatment with a cocaine vaccine might not only block the reinforcing effects of cocaine but also reduce the toxic reactions to cocaine/ethanol combination.

It is clear from the present series of studies that the anti-cocaine actions of a cocaine vaccine emerge gradually over time once immunisation begins. Since the mechanism of the antibody is to bind cocaine in the bloodstream and neutralise its action, self-administration behaviour is reduced through an extinction-like process. Therefore, a cocaine vaccine is not expected to immediately target cocaine craving. Interestingly, ratings of craving increase significantly from inpatient to outpatient treatment, but cocaine-abstinent individuals report lower craving across outpatient treatment and follow-up than moderate and heavy cocaine users.[30] On the basis of these considerations, it is hypothesised that treatment with a cocaine vaccine may eventually help ease cocaine craving and prevent relapse if it extinguishes cocaine use. Adjunct treatment with an anti-craving medication may help in this regard, particularly during the immunisation process. How anti-cocaine antibodies interact with anti-craving medications[31] deserves serious attention as the development of these medications continues and the ability of the vaccine to block the reinforcing effects of cocaine in human clinical trials unfolds.

2. Nicotine

2.1 Vaccines

After the introduction of vaccines against cocaine, efforts to develop a nicotine vaccine soon followed. Even with recent advances in behavioural and pharmacological treatments for smoking cessation, the vast majority of individuals who try to quit smoking will fail. A nicotine antagonist approach through the development of a nicotine vaccine would provide an attractive alternative to substitute medications by preventing relapse when tobacco is used.

In 1997, Pentel and colleagues described the first nicotine vaccine for which a nicotine derivative was conjugated to KLH.[32] After immunising rats with the nicotine vaccine ($3 \times 25\mu g$ over 5 weeks), antibody titres rose to over 10 000. Competition ELISA procedures demonstrated that increasing concentrations of nicotine and the nicotine derivative increased the percent inhibition of antibody binding in a concentration-dependent manner, thus demonstrating their ability to bind to the antibody. The inactive nicotine metabolites, nicotine-N-oxide and cotinine, did not appreciably bind to the antibody with concentrations up to 10^{-2} mol/L. Furthermore, anti-nicotine antibodies did not recognise the structurally dissimilar compounds propranolol and acetylcholine. The nicotine binding capacity of anti-nicotine antibodies after active immunisation (1.3 μmol/L) exceeds the venous plasma levels of nicotine (up to 0.26

μmol/L) and is nearly equal to the arterial plasma levels reported in humans after smoking one to two cigarettes.[33,34] Forty minutes after intravenous administration of nicotine 0.03 mg/kg, there were 4- to 6-fold greater concentrations of nicotine in the plasma of immunised animals but there were no differences in brain levels of nicotine. However, when levels were examined at a more clinically relevant time point (3 minutes after intravenous nicotine administration), brain nicotine concentrations were reduced by 36%, while plasma concentrations raised 3- to 6-fold.[35] The pharmacokinetics are similar even after five repeated doses of nicotine,[36] or after long-term exposure to nicotine before and during immunisation.[37]

To show the effectiveness of anti-nicotine antibodies for altering the behavioural effects of nicotine, nicotine polyclonal antibodies (50–150mg) were initially passively administered to rats.[38] Antibody treatment dose-dependently attenuated nicotine-induced increases in systolic blood pressure and completely prevented nicotine-induced increases in locomotor activity measured 25 hours later. Specificity of the antibodies for nicotine was demonstrated by the failure of antibody treatments to modify cocaine-induced increases in locomotor activity. In nicotine-dependent rats, passive administration of 150mg of nicotine antibodies also prevented nicotine reversal of abstinence signs.[39]

To test the effects of the nicotine vaccine, nicotine-induced seizures were examined in rats. Immunisation reduced the incidence of seizure induced by a high (2 mg/kg) dose of nicotine.[40] The nicotine vaccine was even more effective in preventing seizures if rats were first pre-exposed to nicotine (1 mg/kg/day for 6 days) before the high dose nicotine challenge. This nicotine abuse vaccine began human testing in early 2002 by Nabi Biopharmaceuticals, Boca Raton, Florida, USA under the trade name NicVAX™[1]. NicVAX™ is a nicotine conjugate vaccine, conjugated to a carrier protein, recombinant exoprotein A (rEPA). In the phase I safety and immunogenicity trial, 20 healthy, non-smoker adults were randomly assigned to receive either an intramuscular injection of 200μg of NicVAX™ or placebo. Blood samples showed that a single dose of NicVAX™ resulted in a rapid immune response (within 7 days of vaccination) and generated substantial amounts of nicotine specific antibodies that were maintained or continued to increase through 60 days after vaccination. Adverse effects included mild to moderate local reactions to vaccination that were temporary and required no therapeutic intervention. On the basis of these preliminary findings, Nabi plans to initiate additional clinical trials of NicVAX™ in smokers and ex-smokers in late 2002.[41]

In addition to this nicotine abuse vaccine, at least three other nicotine abuse vaccines are currently under development. Xenova Group plc began phase 1 clinical testing with TA-NIC™ (a nicotine derivative coupled to rec cholera toxin B) in September 2001. The vaccine's safety, tolerability and immunogenicity were investigated in 60 Belgian volunteers, and preliminary results in both smokers and non-smokers have shown the vaccine to be safe and well tolerated both systemically and locally. The vaccine was administered by intramuscular injection and investigated at two different dose levels in a variety of dose administration regimens. The vaccine generated a specific anti-nicotine response, which is especially important in preventing nicotine from reaching the brain. [42] This vaccine was originally developed by ImmuLogic Pharmaceutical Corporation, Waltham, Massachusetts, USA and Cantab Pharmaceuticals plc, Cambridge, UK, and pre-clinical studies demonstrated that the vaccine produced high titre nicotine-specific antibodies in mice and altered the pharmacokinetic distribution of a nicotine challenge.[43] Specifically, one minute after an intravenous bolus of nicotine, nicotine levels in the brain decreased while plasma levels increased. Thus, the antibodies may have the capacity to block the psychoactive effects of nicotine.

Researchers at the Karolinska Institute in Sweden are using a similar approach to actively immunise against nicotine using a nicotine-KLH conju-

1 Use of tradename is for identification purposes only and does not imply endorsement.

gate.[44] The antibodies formed recognised nicotine and the minor metabolite nornicotine, but not the major metabolites cotinine or nicotine-N-oxide. Immunisation in rats showed a reduction in the outflow of dopamine (reward signal) in the nucleus accumbens shell. In addition, Janda and colleagues are currently developing a nicotine addiction programme that consists of active immunisation with a nicotine vaccine to counteract the primary target nicotine and passive administration of monoclonal antibodies to counteract the secondary targets nornicotine and cotinine.[45] In their published report, the synthesis of the vaccine and monoclonal antibodies was described.

In contrast to the pre-clinical work performed with cocaine vaccines and antibodies, no nicotine self-administration studies, where nicotine is repeatedly available, have been reported to date. Although clinical trials with a nicotine vaccine have proceeded without self-administration data being available, it has been suggested[32] that nicotine addiction is a better candidate than cocaine addiction for a vaccine treatment approach because the daily dose of nicotine consumed (~37 mg/day) is lower than the daily dose of cocaine consumed (~1 g/day). Therefore, if antibody titres were high, it would take considerably more effort to saturate anti-nicotine antibody levels and surmount nicotine antagonism by increases in nicotine dose.

2.2 Therapeutic Potential

As an ex-smoker, my personal view is that the best point to immunise with a nicotine vaccine is at a time when peak immunity coincides with abatement of withdrawal symptoms and craving. The majority of individuals attempting to quit smoking can remain smoke free during the first few weeks of abstinence with the help of nicotine replacement therapy, which lessens the severity of withdrawal symptoms and craving.[46] However, the majority of smokers undergoing nicotine replacement relapse between week 4 and week 15 of smoking cessation as the urge to smoke becomes more pronounced.[46,47] Relapse occurs when individuals, even motivated ones, convince themselves that they can 'handle' smoking one cigarette. Feeling the effects of that single cigarette is often sufficient to trigger continued use. However, if the effects of that first cigarette after abstinence are blocked, smoking will fail to prime further use of nicotine. A possible danger of immunising when the urge to smoke is constantly high (either without nicotine replacement therapy or after the first few weeks of nicotine replacement therapy) is that individuals might be more inclined to surmount the anti-nicotine antibodies by applying several nicotine patches before smoking. Extinguishing the reinforcing effects of nicotine at a critical time point in the nicotine withdrawal process may be crucial to the overall success of nicotine vaccines.

3. Phencyclidine

3.1 Monoclonal Antibody Fragments

First synthesised in 1986 by Owens and colleagues, phencyclidine (PCP)-specific antigen-binding fragments (Fab) were found to increase the percentage of bound PCP in the serum of dogs as well as cause a dramatic redistribution of PCP to the plasma fraction.[48] These findings were later confirmed in rats with anti-PCP Fab having an affinity of 1.8 nmol/L.[49,50] As PCP has no known antagonists, it was suggested that high affinity anti-PCP Fab could be used to reverse the toxicity of PCP, especially in cases of overdose.

In pre-clinical tests of PCP toxicity in rats (1 mg/kg intravenously), the increases in locomotion and ataxia produced by PCP were rapidly reversed to baseline values at doses 1–3 times the mole-equivalent dose of PCP.[51] The antibody fragments were specific to PCP because the behavioural effects of the structurally dissimilar PCP-like drug dizocilpine (MK-801) were not influenced by anti-PCP Fab treatment. As the concentration of Fab-bound PCP increased in the serum, the concentrations of PCP in the brain (23% of control), fat (24% of control), heart (52% of control) and testis (12% of control) decreased. Concentrations of PCP in the kidney, where the drug is excreted, increased above control levels.[52] Thus, PCP is

rapidly removed from the brain after anti-PCP Fab treatment, which accounts for the rapid reversal of its toxic effects.

However, as the effects of anti-PCP Fab are short-lived (elimination half-life of 9.4 hours), the more recent development of anti-PCP IgG with an elimination half-life of 15.4 days offers an improved pharmacokinetic profile.[53] In this report, a single mole-equivalent dose of anti-PCP IgG protected the brain from an 18mg/kg/day dose of PCP for approximately 4 weeks.

3.2 Therapeutic Potential

Individuals who use PCP for long periods report memory loss, difficulties with speech and thinking, depression and weight loss[54] High doses of PCP can cause seizures, coma and death.[55] According to the 1996 National Household Survey on Drug Abuse,[54] 3.2 percent of the population aged 12 and older have used PCP at least once. Lifetime use of PCP was higher among those aged 26 through 34 years (4.2%) than for those 18 through 25 (2.3%) and those 12 through 17 (1.2%). Although the use of PCP, overall, is on the decline, the low incidence of use still warrants proper medical intervention, especially in overdose cases. Treatment with high affinity anti-PCP antibodies may be the best line of defence in such patients.

One suggestion is that more attention be focused on the development of anti-ketamine antibodies. The chemical structure and mechanism of action of ketamine are similar to those of PCP, as are its effects on behaviour.[56] Ketamine is marketed as a dissociative anaesthetic and the source for its use on the street is diverted pharmaceutical products. The recent placement of ketamine on the US Schedule III controlled substance list (generally, a drug with moderate potential for abuse but having a currently accepted medical use in treatment in the US. Its abuse, however, may lead to severe psychological or physical dependence) attests to its growing use and abuse, particularly at raves and similar club drug-type events. At this time it is not clear if anti-PCP antibodies will bind ketamine (based on structural similarities) or if novel anti-ketamine antibodies will need to be developed. Recently, Owens and colleagues introduced the concept of developing antibodies to treat toxicity caused by classes of drugs as well as by individual drugs.[57]

4. Methamphetamine

4.1 Vaccines

As with cocaine, no effective pharmacological treatments exist for methamphetamine abuse. This is a concern because methamphetamine has become a worldwide major drug of abuse.[58] It is for this reason Owens and colleagues sought to develop a methamphetamine vaccine.[59] The vaccine was synthesised by conjugating S-(+)-4(5-carboxypentyl)methamphetamine to KLH. In rats immunised with the conjugate (200μg × 3 over a 6-week period), anti-methamphetamine antibody titres rose to over 10 000 and remained at this level throughout the 53-day testing period. Antibody titres and affinities were the same whether or not methamphetamine was present during the immunisation period. However, the locomotor activating effects of a very high dose of methamphetamine (3 mg/kg intraperitoneally) were not antagonised in rats immunised with the above conjugate. It was suggested that the S-(+)-4(5-carboxypentyl)methamphetamine – KLH conjugate was not optimal for an active immunisation protocol against high doses of methamphetamine. Work continues in this area and thus it is too early to ascertain the therapeutic potential of an anti-methamphetamine vaccine.

5. Ethical and Legal Implications

Who gets immunised? Do we immunise children with drug-specific vaccines at the same time we protect them against mumps, rubella and pertussis, and then provide periodic boosts into adulthood? Do parents have the right to choose immunisation with drug-specific vaccines for their children? Do we force or coerce the pregnant drug abuser or the incarcerated drug abuser to undergo immunisation with drug-specific vaccines? In in-

dividuals who voluntarily choose to be immunised, how can confidentiality be assured about former illegal drug use when drug-specific antibodies will remain detectable in the blood for years? Should drug-specific antibodies automatically be administered to reverse the effects of drug overdose in medical emergencies? The answers to these questions have both ethical and legal implications. With the exception of a nicotine vaccine, use of drug-specific vaccines and antibodies carries potential for stigmatisation, discrimination and coercion.[60] Therefore, deciding who get immunised requires careful consideration.

As parents, we constantly make choices regarding our children, including decisions about immunisation against disease. Although drug addiction is a disease, immunising against drug addiction is not equivalent to immunising against an infectious disease. With infectious diseases, we protect against the small possibility that our child will be exposed unwittingly at one time or another to an infectious agent. When individuals choose to take a drug of abuse, they expose themselves to the drug and generally do so multiple times. We need to consider the impact on the immunised child who, as a teenager, decides to experiment with a drug against which he or she was previously immunised. Either further use of the drug is abandoned, or alternatively, very large drug doses are consumed in an attempt to saturate the antibodies and surmount the antagonism. In this latter situation, parents risk producing an offspring who develops an overly expensive drug habit. Notwithstanding the medical complications that may arise from sustained high dose drug use, there should be concern that the child is liable to engage in new and, most probably, illegal activities to support his or her drug habit. Parents may get more than they bargained for if they choose to immunise their child against drugs of abuse.

Moreover, imagine a scenario in which a convicted criminal is told that being immunised against drugs of abuse is a condition for probation or parole. Is this form of coercion legal? Currently, individuals abusing alcohol and other drugs are often required to attend Alcoholics Anonymous meetings or other drug-related treatment programmes as a condition for parole. It is even mandated for some to take medication (for example, naltrexone for narcotic abuse; disulfiram for alcohol abuse). However, there are limits to the conditions that are acceptable for probation and parole.[60] Is mandatory vaccination against drugs of abuse cruel or unusual punishment, given that antibodies will remain detectable in the blood for years? It is highly likely that if the criminal justice system considers using court mandated drug-specific vaccines, the final decision for the legality of their use may rest in the hands of the US Supreme Court. But, need this issue stretch this far?

Considering the scientific view that drug-specific vaccine and antibody treatments might be successful only in individuals who are highly motivated to quit using illegal drugs all together, immunisation might only benefit individuals who give their consent voluntarily. Coercion will not likely provide the type of motivation that is required for an individual to quit using illegal drugs. Individuals should be fully informed about the consequences of taking large doses of a drug in an attempt to 'short circuit' the antibody response. They should also be informed of possible discrimination and stigmatisation by having their past illegal drug use revealed in a simple blood test.

Perhaps the least challenging ethical and legal issue is the use of drug-specific monoclonal antibodies to rapidly reverse drug overdose in emergency situations. In general, passively administered monoclonal antibodies remain in the system for only a short period of time, assuming sufficient renal clearance. Such treatments would not carry the potential for stigmatisation and discrimination in the long-term.

6. Conclusions

There is clearly a need for new treatment options for drug addiction because the relapse rate among drug abusers seeking treatment is quite high. Although pre-clinical studies attest to the feasibility of vaccine approaches for treating addic-

tion to various drugs, cautious optimism should be exercised because it is often the case that candidate therapeutics fail to show suitable efficacy in clinical trials. However, if clinical trials demonstrate the safety and efficacy of treating drug addiction with vaccine approaches, then their approval for use in humans will necessitate consideration of issues that reach beyond the realm of science.

Acknowledgements

This review is dedicated to the memory of Dr Marian Fischman, whose insights for the clinical testing of the cocaine vaccine TA-CD will be greatly missed.

The National Institute on Drug Abuse (USA) is acknowledged for funding (DA11716) used to assist in the preparation of this manscript. No conflicts of interest are present in the content of this manuscript.

References

1. Bonese KF, Wainer BH, Fitch FW, et al. Changes in heroin self-administration by a rhesus monkey after morphine immunisation. Nature 1974; 252: 708-10
2. Carroll FI, Howell LL, Kuhar MJ. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. J Med Chem 1999; 42: 2721-36
3. Akbarzadeh A, Mehraby M, Zarbakhsh M, et al. Design and synthesis of a morphine-6-succinyl-bovine serum albumin hapten for vaccine development. Biotechnol Appl Biochem 1999; 30: 139-45
4. Morell V. Enzyme may blunt cocaine's action. Science 1993; 259: 1828
5. Landry DW, Zhao K, Yang GX, et al. Antibody-catalyzed degradation of cocaine. Science 1993; 259: 1899-901
6. Yang G, Chun J, Arakawa-Uramoto H, et al. Anti-cocaine catalytic antibodies: a synthetic approach to improved antibody diversity. J Am Chem Soc 1996; 118: 5881-90
7. Mets B, Winger G, Cabrera C, et al. A catalytic antibody against cocaine prevents cocaine's reinforcing and toxic effects in rats. Proc Natl Acad Sci U S A 1998; 95: 10176-81
8. Baird TJ, Deng SX, Landry DW, et al. Natural and artificial enzymes against cocaine. I: Monoclonal antibody 15A10 and the reinforcing effects of cocaine in rats. J Pharmacol Exp Ther 2000; 295: 1127-34
9. Basmadjian GP, Singh S, Sastrodjojo B, et al. Generation of polyclonal catalytic antibodies against cocaine using transition state analogs of cocaine conjugated to diptheria toxoid. Chem Pharm Bull (Tokyo) 1995; 43: 1902-11
10. Cashman JR, Berkman CE, Underiner GE. Catalytic antibodies that hydrolyze (-): cocaine obtained by a high-throughput procedure. J Pharmacol Exp Ther 2000 293: 952-61
11. Bagasra O, Forman LJ, Howeedy A, et al. A potential vaccine for cocaine abuse prophylaxis. Immmunopharmacology 1992; 23: 173-9
12. Carrera MRA, Ashley JA, Parsons LH, et al. Suppression of psychoactive effects of cocaine by active immunization. Nature 1995; 378: 727-30
13. Carrera MRA, Ashley JA, Zhou B, et al. Cocaine vaccines: antibody protection against relapse in a rat model. Proc Natl Acad Sci U S A 2000; 97: 6202-6
14. Carrera MR, Ashley JA, Wirsching P, et al. A second-generation vaccine protects against the psychoactive effects of cocaine. Proc Natl Acad Sci U S A 2001; 98: 1988-92
15. Ettinger RH, Ettinger WF, Harless WE. Active immunization with cocaine-protein conjugate attenuates cocaine effects. Pharmacol Biochem Behav 1997; 58: 215-20
16. Johnson MW, Ettinger RH. Active cocaine immunization attenuates the discriminative properties of cocaine. Exp Clin Psychopharmacol 2000; 8: 163-7
17. Fox BS, Kantak KM, Edwards MA, et al. Efficacy of a therapeutic cocaine vaccine in rodent models. Nat Med 1996; 2: 1129-32
18. Evans SM, Cone EJ, Henningfield JE. Arterial and venous cocaine plasma concentrations in humans: relationship to route of administration, cardiovascular effects and subjective effects. J Pharmacol Exp Ther 1996; 279: 1345-56
19. Kantak KM, Collins SL, Lipman EG, et al. Evaluation of anticocaine antibodies and a cocaine vaccine in a rat self-administration model. Psychopharmacology 2000; 148: 251-62
20. Kantak KM, Collins SL, Bond J, et al. Time course of changes in cocaine self-administration behavior during immunization with the cocaine vaccine IPC-1010. Psychopharmacology 2001; 153: 334-40
21. Kosten TR, Rosen M, Bond J, et al. Human therapeutic cocaine vaccine: safety and immunogenicity. Vaccine 2002; 20: 1196-204
22. TA-CD. Available from URL: http://www.xenova.co.uk/dc_ta_cd.html [Accessed 2002 Jan 15]
23. Anti-cocaine addiction vaccine released from clinical hold phase IIa study results announced [online]. Available from URL: http://www.xenova.co.uk/PressReleases/pr_20010709_01.html [Accessed 2002 Jan 15]
24. Schabacker DS, Kirschbaum KS, Segre M. Exploring the feasibility of anti-idiotypic cocaine vaccine: analysis of the specificity of anticocaine antibodies (Ab1) capable of inducing Ab2beta anti-idiotypic antibodies. Immunology 2000; 100: 48-56
25. Washton AM, Stone-Washton N. Abstinence and relapse in outpatient cocaine addicts. J Psychoactive Drugs 1990; 22: 135-47
26. Song N, Parker RB, Laizure SC. Cocaethylene formation in rat, dog and human hepatic microsomes. Life Sci 1999; 64: 2101-8
27. McCance-Katz EF, Kosten TR, Jatlow P. Concurrent use of cocaine and alcohol is more potent and potentially more toxic than use of either alone: a multiple-dose study. Biol Psychiatry 1998; 44: 250-9
28. Raven MA, Necessary BD, Danluck D, et al. Comparison of the reinforcing and anxiolytic effects of intravenous cocaine and cocaethylene. Exp Clin Psychopharmacol 2000; 8: 117-24
29. McKay JR, Alterman AI, Rutherford MJ, et al. The relationship of alcohol use to cocaine relapse in cocaine dependent patients in an aftercare study. J Stud Alcohol 1999; 60: 176-80
30. Bordnick PS, Schmitz JM. Cocaine craving: an evaluation across treatment phases. J Subst Abuse 1998; 10: 9-17
31. Kuhar MJ, Carroll FI, Bharat N, et al. Anticocaine catalytic antibodies have no affinity for RTI compounds: implications for treatment. Synapse 2001; 41: 176-8
32. Hieda Y, Keyler DE, Vandevoort JT, et al. Active immunization alters the plasma nicotine concentration in rats. J Pharmacol Exp Ther 1997; 283: 1076-81

33. Benowitz NL, Hall SM, Herning RI, et al. Smokers of low yield cigarettes do not consume less nicotine. N Engl J Med 1983; 309: 139-42
34. Henningfield JE, Stapleton JM, Benowitz NL, et al. Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend 1993; 33: 23-9
35. Hieda Y, Keyler DE, Vandevoort JT, et al. Immunization of rats reduces nicotine distribution to brain. Psychopharmacology 1999; 143: 150-7
36. Keyler DE, Hieda Y, Peter J, et al. Altered disposition of repeated nicotine doses in rats immunized against nicotine. Nicotine Tob Res 1999; 1: 241-9
37. Hieda Y, Keyler DE, Ennifar S, et al. Vaccination against nicotine during continued nicotine administration in rats: immunogenicity of the vaccine and effects on nicotine distribution to brain. Int J Immunopharmacol 2000; 22: 809-19
38. Pentel PR, Malin DH, Ennifar S, et al. A nicotine conjugate vaccine reduces nicotine distribution to brain and attenuates its behavioral and cardiovascular effects in rats. Pharmacol Biochem Behav 2000; 65: 191-8
39. Malin DH, Lake JR, Lin A, et al. Passive immunization against nicotine prevents alleviation of nicotine abstinence syndrome. Pharmacol Biochem Behav 2001; 68: 87-92
40. Tuncok Y, Hieda Y, Keyler DE, et al. Inhibition of nicotine-induced seizures in rats by combining vaccination against nicotine with chronic nicotine infusion. Exp Clin Psychopharmacol 2001; 9: 228-34
41. Nabi Biopharmaceuticals reports encouraging preliminary results of NicVAX™ clinical trial [online]. Available from URL: http://www.nabi.com/releases/100302.html [Accessed 2002 Dec 30]
42. Successful results of phase I trial for TA-NIC: first evaluation of anti-nicotine vaccine in man. Available from URL: http://www.xenova.co.uk/pressreleases/pr_20020614_01.html [Accessed 2002 Dec 30]
43. Kasaian M. Development of a vaccine for treatment of nicotine dependence [abstract]. NIDA Symposium on Peripheral Blockers as Treatments for Substance Abuse and Dependence. 1998 Apr 27-28. Available from URL: http://165.112.78.61/meetsum/peripheral/index.html (Accessed 2002 Jan 15)
44. de Villiers S, Lindblom N, Kalayanov G, et al. Active immunisation against nicotine can suppress the nicotine-induced stimulation of brain dopaminergic reward pathways [abstract 192.12]. Soc Neurosci 2000; 26 (Pt 1): 529
45. Isomura S, Wirsching P, Jandra KD. An immunotherapeutic program for the treatment of nicotine addiction: hapten design and synthesis. J Org Chem 2001; 66: 4115-21
46. West R, Hajek P, Nilsson F, et al. Individual differences in preferences for and responses to four nicotine replacement products. Psychopharmacol 2001; 153: 225-30
47. Gross J, Stitzer ML. Nicotine replacement: ten-week effects on tobacco withdrawal symptoms. Psychopharmacol 1989; 98: 334-41
48. Owens SM, Mayersohn M. Phencyclidine-specific fab fragments alter phencyclidine disposition in dogs. Drug Metab Dispos 1986; 14: 52-8
49. McClurkan MB, Valentine JL, Arnold L, et al. Disposition of a monoclonal anti-phencyclidine fab fragment of immunoglobulin G in rats. J Pharmacol Exp Ther 1993; 266: 1439-45
50. Valentine JL, Arnold LW, Owens SM. Anti-phencyclidine monoclonal fab fragments markedly alter phencyclidine pharmacokinetics in rats. J Pharmacol Exp Ther 1994; 269: 1079-85
51. Valentine JL, Mayersohn M, Wessinger WD, et al. Antiphencyclidine monoclonal fab fragments reverse phencyclidine-induced behavioral effects and ataxia in rats. J Pharmacol Exp Ther 1996; 278: 709-16
52. Valentine JL, Owens SM. Antiphencyclidine monoclonal antibody therapy significantly changes phencyclidine concentrations in brain and other tissues in rats. J Pharmacol Exp Ther 1996; 278: 717-24
53. Proksch JW, Gentry WB, Owens SM. Anti-phencyclidine monoclonal antibodies provide long-term reductions in brain phencyclidine concentrations during chronic phencyclidine administration in rats. J Pharmacol Exp Ther 2000; 292: 831-7
54. Nature and effects of ketamine [online]. Available at URL: http://165.112.78.61/ResearchReports/hallucinogens/halluc4.html [Accessed 2002 Jan 15]
55. Baldridge EB, Bessen HA. Phencyclidine. Emerg Med Clin North Am 1990; 8: 541-50
56. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction 2001; 96: 749-60
57. Hardin JS, Wessinger WD, Proksch JW, et al. Pharmacodynamics of a monoclonal antiphencyclidine fab with broad selectivity for phencyclidine-like drugs. J Pharmacol Exp Ther 1998; 285: 1113-33
58. Murray JB. Psychophysiological aspects of amphetamine-methamphetamine abuse. J Psychol 1998; 132: 227-37
59. Byrnes-Blake KA, Carroll FI, Abraham P, et al. Generation of anti- (+)methamphetamine antibodies is not impeded by (+)methamphetamine administration during active immunization of rats. Int J Immunopharmacol 2001; 1: 329-38
60. Cohen PJ. Immunization for prevention and treatment of cocaine abuse: legal and ethical implications. Drug Alcohol Depend 1997; 48: 167-74

Correspondence and offprints: Professor *Kathleen M. Kantak*, Department of Psychology, Boston University, 64 Cummington St, Boston, MA 02215, USA.
E-mail: kkantak@bu.edu