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Development of Active and Passive Human Vaccines to Treat Methamphetamine Addiction

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Abstract

Methamphetamine (METH) abuse is a major worldwide epidemic, with no specific medications for treatment of chronic or acute effects. Anti-METH antibodies have the potential to save lives and reduce the crippling effects of METH abuse. While they are not expected to be the magic bullet to immediately cure addiction, immunotherapy could provide a breakthrough medication to continuously block or attenuate METH effects during a comprehensive addiction recovery plan. A unique challenge for METH antibody antagonists is the need to protect the brain from the complex direct and indirect adverse effects of long-term METH use. To meet this challenge, a new generation of passive monoclonal antibodies and active immunization therapies are at an advanced stage of preclinical development. Both of these vaccines could play an essential role in a well planned recovery program from human METH addiction by providing long-lasting protection from the rewarding and reinforcing effect of METH.

Keywords

Addiction; amphetamines; drug abuse; methamphetamine; monoclonal antibody; vaccines

INTRODUCTION

Stimulant abuse, especially methamphetamine (METH) abuse, continues to be a major problem in the USA and world-wide. The number of patients in the USA admitted to treatment for METH or amphetamine as their primary substance of abuse increased over 400% from 1993-2003.¹ In addition, 58% of law enforcement agencies in 45 states indicated that METH is the greatest drug problem.²

METH use results in a complex constellation of acute and chronic effects that involve many organ systems in the body (Table 1). The profound central nervous system (CNS) effects of METH include a sense of increased energy, self-confidence, and well-being; as well as heightened awareness, appetite suppression, euphoria, and increased sexual performance. These effects are significantly reinforcing, and undoubtedly play a role in establishing addiction to METH. The adverse biological effects of METH may be sudden, resulting in acute organ system dysfunction, or they may be longer lasting, resulting in addiction or permanent tissue damage. Effects on the cardiovascular system (CVS), CNS and toxic metabolic effects, such as hypertension, tachycardia, myocardial infarction, strokes, seizures and acute renal

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failure, pose the most serious acute medical problems.³⁻⁶ However, chronic effects such as increased vulnerability to infectious diseases and long-term neurotoxicity play an important role in the societal impact from abuse-related problems.^{6, 7}

In the past, discovery of small molecule agonists like methadone for the treatment of opiate addiction has been the mainstay of medications discovery for the treatment of addiction. In addition, it is not unusual for these addiction medications to have significant side effects including the potential for causing their own addiction (e.g., methadone). The broad and fairly non-selective mechanism of METH action suggests it will be difficult to find a similar selective high affinity small molecule agonist or antagonist to treat METH addiction. This is especially true since none of the METH transporter effects are mitigated through a high affinity, uniquely METH specific site. The broad and non-selective action for METH and similar stimulant drugs of abuse may also explain why no effective and non-addictive medication for stimulant addiction has been discovered.

METH inhibits the reuptake of monoamine transmitters at the nerve membrane via reverse transport action at monoamine transporters,⁸⁻¹¹ increases the release of newly synthesized catecholamines from the nerve¹², and interferes with the vesicular monoamine transporter to increase the amount of transmitter in the nerve ending. The vesicular monoamine transporter is the main transporter involved in sequestration of dopamine (DA), serotonin (5HT), and norepinephrine (NE) into vesicles for storage and release.¹³⁻¹⁵ DA is the most commonly discussed monoamine to be affected by METH use. However, METH's complex constellation of effects likely results from complex interactions with multiple neurotransmitters; including DA, 5HT, NE, gamma-aminobutyric acid (GABA), and histamine. Furthermore, these neurotransmitter systems are intimately interrelated and co-regulated.¹⁶ This decreases the likelihood even more of discovering a single receptor or binding site target at which a small molecule agonist or antagonist could be effective. This medical hypothesis is likely true for both CNS and CVS effects, the organ systems most prominently affected by METH.

IMMUNIZATION AS A TREATMENT FOR DRUG ABUSE

Immunotherapies, either active immunization or passive administration of anti-METH monoclonal antibodies (mAbs), have a totally different mechanism and therapeutic utility when compared to small molecule agonists or antagonists. They do not rely on inhibition of METH binding at specific receptors within the CNS. Their primary action is to confine METH distribution and block its effects through high affinity binding primarily in the bloodstream. This is accomplished without antibody penetration into the CNS. Indeed, antibodies are blocked from penetrating the tight junctions of the CNS vesicular blood-brain barrier by their large size.¹⁷ In essence, anti-METH antibodies produce a sustainable equilibrium shift of METH out of the brain and into the blood stream, as measured by substantial reductions in METH brain concentrations over time and substantial increases in METH serum concentrations over time (Figure 1).^{18, 19} These antibody-induced reductions in METH volume of distribution, clearance from the blood stream, and substantially increased serum (antibody) protein binding are why antibody medications are classified as pharmacokinetic antagonists; that is, they favorably change the concentration-time course of METH in multiple organ systems. A classic example of this medical approach is treatment with short-acting anti-digoxin antigen binding fragments (Fab) to cure digoxin overdose and cardiac toxicity.²⁰

Hapten design is critical to the development of both active and passive immunization approaches. This is in part because METH is an extremely small molecule with a molecular weight of only 151. Thus, it is near the lower limit of the antigenic size for generation of antibodies. We have conducted extensive structure activity studies of the molecular features of haptens that would stimulate high affinity immune responses to METH because high affinity

for METH is our most important goal. Furthermore, we wanted to understand how to generate high affinity antibodies for METH, (+)-amphetamine and (+)-3,4-methylenedioxymethamphetamine (the positive isomer in the racemic mixture commonly known as ecstasy) with the use of one or more haptens. All three of these structurally related drugs have significant abuse potential. It is established that the (+) or *d*-isomers of METH-like compounds produce significantly more psychomimetic effects, locomotor activity, stereotyped behavior, and monoamine oxidase inhibition than the (-) or *l*-isomers.^{21, 22} For this reason, we design our METH-like haptens to be chemical mimics of the (+)-isomers of these drugs.

While all of our haptens produce reasonably high affinity antibodies, we find that longer spacer arms between the METH moiety and site at which it is coupled to the protein antigen allow more flexibility in the hapten. This in turn appears to produce broader recognition of METH-like structures, without the loss of stereoselectivity for (+)METH versus (-)METH. Among five different METH-like haptens that we have extensively characterized, we find a hapten called MO10-METH leads to the best anti-METH immunological response (i.e., affinity and specificity). This hapten contains a 10 molecule linker which is attached at the meta position of the METH molecule. At the distal end of this linker is a carboxylic moiety for use in the formation of a covalent peptide bond with the lysine groups of antigenic proteins (e.g., bovine serum albumin, and ovalbumin). Studies of the use of this and other haptens for active immunization, along with several candidate antigenic carrier proteins and adjuvants for use in humans are currently under investigation by our group. These vaccines are being screened in behavioral models to test their ability to prevent METH-induced relapse to METH use, self-administration and locomotion effects in rodent models of human METH addiction.

In active immunization, repeated administration of a METH-like hapten-protein conjugate is used to develop a long-lasting immunological memory against the drug of abuse.²³ This immunological memory leads to a more rapid response to future booster injections, and due to its longevity and relative low cost to the patient it could be a viable approach for use in relapse prevention.

Preclinical behavioral studies in rodents and non-human primates of active immunizations against cocaine and nicotine show the potential benefit of this approach. Immunization of rats with a high dose of anti-cocaine vaccine or passive immunization with mAb leads to a 50-75% reduction in several indicators of addiction behaviors including cocaine self-administration,^{24, 25} reinstatement of cocaine-seeking behavior,²⁶ reduction in cocaine-induced locomotor activity (up to 70%), and stereotypy after three vaccine boosts.²⁷ In rhesus monkeys, vaccination leads to decreased behavioral effects of cocaine in a food maintained behavioral paradigm.²⁸ Vaccination against nicotine attenuates nicotine self-administration²⁹ and locomotor sensitization to nicotine³⁰ in rats. These encouraging preclinical findings for both cocaine and nicotine addictions have prompted the transition of active vaccination studies from preclinical to clinical studies, in which promising results were obtained for cocaine^{31, 32} and nicotine.^{33, 34}

While our laboratory has used active immunization in mice as a precursor to the production of anti-phencyclidine (PCP) and anti-METH mAbs for over two decades, until recently almost no studies were performed to investigate the protective effects of active immunization against METH-like haptens. In the first study to treat METH abuse with active immunization,²³ our group found that immunization with a METH-like hapten (designated PO6-METH) coupled to keyhole limpet hemocyanin (KLH) in rats produced significant anti-METH antibody titers after three active vaccinations over 53 days, but it did not attenuate the METH-induced locomotor activity resulting from twice weekly intraperitoneal injections of 3 mg/kg METH. However, the main hypothesis of the studies was to determine if the immune response against the PO6-METH hapten would be adversely affected by repeated and frequent METH use. The

3 mg/kg dose of METH in rats was medically equivalent to an extremely excessive human use of the drug. Thus, the active immunization approach was not expected to provide significant protection against METH-induced effects. Nonetheless, the results of the study demonstrated that the immunological response to the METH-like antigen was sustained compared to the immunological control animals (without METH treatment), and the affinity of the polyclonal antibodies for METH did not differ from the control. This is an important finding for the active immunization approach for drug addiction since the results demonstrate that taking METH (even at extremely high doses) during the vaccination period has no effect on the generation of high titer and high affinity anti-METH antibodies.

Passive immunization refers to the administration of pre-generated antibodies. Historically, the antibodies for passive immunization against small molecular weight molecules were generated by immunizing animals with a drug-hapten coupled to an antigenic protein carrier. The purified polyclonal anti-drug antibodies were then administered to patients to block drug effects. In our laboratory, anti-METH mAbs are selected from hybridoma cell lines produced from hyper-immunized mice,³⁵ or through genetic engineering techniques.³⁶

Preclinical studies also show the therapeutic potential of this approach. Our group has shown that anti-METH mAbs are able to antagonize the locomotor effects of a 1 mg/kg METH dose in rats, when given 30 min after the drug administration¹⁸ in a simulation of a human treatment scenario for drug overdose. The antagonism of the METH-induced locomotor effects in the rats was accomplished by using a high (K_D for METH = 10 nM) and a low affinity mAb (K_D for METH = 250 nM). Not surprisingly, the higher affinity mAb was more effective in reducing METH-induced locomotor effects than was the low affinity mAb¹⁸. When the same mAbs were given as a pretreatment for METH effects at either one, four, or seven days prior to the METH challenge, both mAbs were still effective in reducing METH-induced locomotor activity, but to a lesser degree than when given 30 min after a METH challenge dose.¹⁸

A possible explanation for the time-dependent differences in efficacy lies in the distribution of METH and the antibody at the time of the measurement. In the acute overdose model, the mAb was administered 30 min after the METH dose, thus METH was already distributed into all tissues including the brain.¹⁹ In contrast, when the anti-METH mAb is given prior to the METH challenge (in an experimental model of the protective effects of mAb), the mAb was already fully distributed when METH was administered. In this treatment scenario, the high bolus dose of METH probably temporarily overwhelmed the capacity of the mAb, leading to an initial METH distribution into the brain for the first few minutes followed by a somewhat slower mAb-induced redistribution of the METH back into the blood stream¹⁹ (see Figure 1 for an artist conception of these brain processes). Even though the brain is usually considered to be preferentially protected from drugs of abuse by antibodies,^{18, 19, 37, 38} other organs and organ systems also benefit from mAb treatment. Indeed, organs which have received less METH and have a blood organ barrier (i.e., the brain), seem to benefit the most from mAb treatment, whereas other organs which have high blood flows and receive high doses of METH, seem to adjust slower to the mAb induced re-equilibrium of METH.¹⁹

Behavioral studies of METH-induced locomotor effects also support the hypothesis of some preferential mAb protection of the brain. For example, when a high affinity anti-METH mAb was administered to rats, who were then challenged with METH 1 and 4 days later, locomotor activity was significantly reduced relative to control rats without antibody,³⁹ indicating a removal of METH from the brain. For nicotine, administration of nicotine-specific mAbs in rats leads to decreased brain concentrations of nicotine,⁴⁰⁻⁴² decreased drug key responding in drug discrimination⁴³ and a complete blockage of the effects of nicotine administration to alleviate abstinence syndrome.⁴¹

Aside from reducing locomotor activity, the administration of the anti-METH mAb also decreases the area under the effect versus time curve for METH-induced elevations in blood pressure and heart rate. These results also indicated that a high affinity anti-METH mAb can be effective in multiple organ systems (CNS and CVS) simultaneously.³⁹ Thus, both neuroprotection and cardiovascular protection can result after treatment with anti-METH mAb therapy.

In self-administration preclinical studies in rats, pretreatment with anti-METH mAb has differential effects on METH self-administration. When compared to control responses without mAb, it increases self-administration of a higher METH dose (0.06 mg/kg/infusion), has no apparent effect on a moderate dose (0.03 mg/kg/infusion), and decreases self-administration of a low dose (0.01 mg/kg/infusion) down to saline (control) levels.⁴⁴ These data at first glance suggest a confusing or perhaps partial pharmacokinetic antagonism of METH by the mAb. However, our interpretation of these results is that the mAb administration produced a rightward shift of the entire METH self administration dose-response curve. Thus, the mAb-treated rats experienced lower apparent METH self administration doses than the control (no mAb treatment) rats.

In drug discrimination preclinical trials in pigeons and rats, a low affinity mAb shifted the METH dose-response curve to the right, indicating that higher doses of METH were needed by the animals to perceive a similar discriminative stimulus effect.⁴⁵ This curve shift was achieved with subcutaneous, intraperitoneal and intramuscular injections of METH in rats and/or pigeons, thus providing proof for a generalization of the protective effects of anti-METH mAb in two species. Similarly to the observation with self-administration, the curve-shifting effect of the single dose of anti-METH mAb lasted for 4 to 7 days, then disappeared gradually. This duration of effects in the rats is consistent with the known biological half-life of mouse mAb in rats (i.e., ~ 7 days).⁴⁶ In addition, drug discrimination studies were also used to test the *in vivo* specificity of the anti-METH mAb against the other drugs of abuse. When the anti-METH mAb was tested against PCP, cocaine and amphetamine, there were no drug discrimination effects observed on the dose-response curve for those drugs, indicating a high degree of *in vivo* specificity for anti-METH mAbs.^{45, 47} In contrast, when the anti-METH and anti-PCP mAbs were co-administered to pigeons in behavioral drug discrimination studies, there was a simultaneous, yet drug selective protective effect against each of these drugs.⁴⁷ This is the first study to use a mAb “cocktail” to provide protection against the effects of two drugs at once.

HUMAN APPLICATIONS FOR IMMUNOTHERAPIES

There are two primary indications for the use of immunotherapies in the treatment of human METH abuse. The first is treatment of overdose. This indication will necessarily utilize anti-drug monoclonal antibodies, due to the required rapid onset of therapeutic antibody effects. The second indication is relapse prevention. Passive administration of monoclonal antibodies and active immunization are both candidate medications for this indication.

Clinical Indications for Anti-METH Immunization — Acute Overdose

A variety of pharmacological therapies have been used for treating the acute consequences of METH abuse in humans. None of these, however, are specific for METH — that is, there is no direct antagonist for METH. Pharmacotherapies for acute toxic effects of METH are primarily supportive and symptomatic,^{3, 48} minimizing the symptoms as METH slowly distributes from its active sites to metabolic sites prior to elimination. Because the elimination half-life of METH in humans is about 12 hr,^{49, 50} patients may experience toxic effects (e.g., paranoia, seizures, severe hypertension, tachycardia and dysrhythmias) for many hours after taking METH. Current pharmacological treatment includes (but is not limited to)

administration of sedatives, anti-seizure medications, antihypertensives, and even physical restraints for hours to days while METH is eliminated.^{3, 6} The rapid removal of METH from the brain and other critical organs by a high-affinity anti-METH mAb could significantly reduce the time a patient requires intensive treatment, and in so doing reduce the risk of organ system damage.

Clinical Indications for Anti-METH Immunization — Relapse Prevention

The second major indication for immunotherapeutic intervention is prevention of relapse to METH use. This is a more complex scenario than overdose, but one in which immunotherapies offer a truly novel approach to the treatment of drug abuse.

Current treatments for METH addiction are cognitive behavioral interventions,⁵¹ which are long-term approaches used to modify patient thinking and behaviors, thus improving the ability to avoid drug taking behaviors. Even after successfully completed treatment programs, however, 36% of patients use METH again in the first six months after treatment and another 15% again within 13 months.⁵² Similar behavior modification approaches are used to treat nicotine addiction with modest success (e.g., refs.⁵³⁻⁵⁵). The success of these approaches for nicotine is likely increased by the availability of nicotine replacement therapy or medications to reduce drug craving that can be used in combination with the psychotherapy.⁵³ Non-specific palliative pharmacologic adjuncts can help suppress the depression and anxiety associated with METH withdrawal,⁵⁶ but unfortunately, no replacement therapies or drugs that reduce craving have been discovered or approved for METH.

This high rate of relapse to METH taking behavior may be attributed to the fact that there is no currently available treatment that reduces the pleasurable reinforcing effects of METH. Indeed, a significant factor that is associated with reinforcement of drug use and relapse to drug use (i.e., addiction) is the rapid perception of the intense CNS effects of METH.⁵⁷ By preventing METH from reaching its sites of action in the brain and by removing METH from the CNS, immunotherapies could prevent and reduce the reinforcing effects of METH (Figure 1). Furthermore, because of their lack of CNS effects and low potential for interactions with other drugs, immunotherapies are excellent candidates for use in combination with behavioral approaches. We envision that anti-drug antibody-based therapeutics will become an essential component of a comprehensive, evidenced-based medical treatment plan for relapse prevention. This would include combination of an immunotherapeutic medication with an appropriate counseling or behavioral modification program. Ideally, this treatment approach would result in disease free (i.e., drug free) state for sufficient time to return the patient to a more normal physiologic state and to relearn a sustainable way of life. If (in the future) small molecular weight agonist, antagonist or anti-craving drugs were proven beneficial for METH addiction, they could be combined with the immunotherapy and behavior modification program.

Patient Selection for anti-METH Immunization

An important component of improving the chance of success of immunotherapies in relapse prevention is appropriate selection of patients. Anti-METH immunotherapy is not likely to be successful in patients who are ‘end-stage’ users, who are frequently under the influence, continue to use large amounts of METH, and do not seek treatment. These medications have the greatest chance of success in patients who seek treatment and desire to improve their health and well-being; that is, in patients who are strongly motivated to adhere to a comprehensive medical regimen, but who simply cannot stop METH use by themselves. Indeed most medical treatments would not be successful without some level of patient compliance.

Similar medical scenarios to the treatment of drug abuse are chronic illnesses like high blood pressure and diabetes mellitus, where the ability to adhere to a multi-modal approach is a key to therapeutic success. In the case of diabetes, the administration of insulin by itself reduces blood sugar levels, but unless the patient opts to change his diet, exercise, and monitor his blood sugar, much of the therapeutic benefit of the insulin is lost. Immunotherapy will be beneficial when the user takes METH, because the reduction of the reinforcing and intoxicating effects will help him to make the choice to continue to seek counseling, change his lifestyle, avoid situations that prompt drug use, and strive for general health improvement. Indeed, by binding to METH, immunotherapies have the potential to decrease the untoward health effects of the stimulant.

Preclinical proof that anti-drug mAb have the potential to improve the health of the user comes from long-term studies in our laboratory with an antibody against another stimulant of abuse, PCP. This murine high-affinity (PCP $K_D = 1.3$ nM) anti-PCP mAb (called mAb6B5) is effective at preventing PCP-induced effects, even when the mAb dose is substantially lower than the body burden of PCP.³⁷ In fact, mAb6B5 doses of only 1/100th the PCP body burden can prevent adverse PCP-induced health effects (including weight loss and indicators of physiologic stress), significantly decrease PCP brain concentrations, reverse PCP-induced locomotor effects, and even prevent death from PCP overdose. In this preclinical scenario, the antibody serves as both a treatment for a wide range of medical dangerous issues, as well as serving as a cure for the effects of drug overdose.

While motivation is important in determining patient suitability for anti-drug immunotherapy, other characteristics must be considered in the selection of active vs passive immunization for relapse prevention. The individual's risk of recidivism is important because it takes time for a significant antibody titer to be generated (e.g., 3-8 weeks). For patients who are able to curtail their METH use while the vaccine confers protection, active immunization has potential benefit. There is also likely to be a considerable individual variability in the amount of anti-METH antibody that would be produced, so patients would have to be monitored for an antibody response. For those at high risk for recidivism or for those who do not generate an adequate response, the immediate protection afforded by passive immunization will be advantageous. In addition, dosing of the antibody can be tailored to the need of the patient, with higher and frequent doses given at critical times, such as increased drug craving or during stressful life events. Other advantages of passive immunization in this scenario include the ability to control the quality and uniformity of the antibody formulation. The major disadvantage of passive immunization with mAbs is the high cost of the medication.

Similarly, the overall health of the individual's immune system is an important patient characteristic in the selection of active vs passive approaches. While an effective active vaccine would be expected to stimulate adequate antibody titers in reasonably healthy individuals, a substantial proportion of METH users may not have sufficient immune system reserves to generate effective amounts of anti-METH antibodies. This is because intravenous drug use is a major cause of HIV transmission, which compromises immune system function,⁵⁸ and because long-term METH use is also associated with immune suppression.⁵⁹ A major advantage of passive mAb therapy is the effectiveness in patients with compromised immune systems.

Safety Considerations for Immunotherapies in Humans

Because anti-METH mAb medications work by reducing brain METH concentrations, and because the mAb molecules are too large to cross the blood—brain barrier, they will not likely directly interfere with normal neurotransmitter action.^{18, 60} In addition, the anti-METH mAb medications developed to date do not bind to or inhibit the actions of normal endogenous ligands, including DA, NE, and other molecules or medications.⁶¹ In rat models, behavior

normalizes with removal of METH from the brain, suggesting that these mAb medications minimally alter neurotransmitter function. Thus, anti-METH immunotherapy is not likely to result in further functional deficits. Indeed, it could be argued that antibody-induced removal of METH from the brain might allow for a more normal recovery than treatment with a small molecule competitive agonist or antagonist.

Other preclinical studies in rats with anti-METH mAbs show that even high intravenous doses of 1,000 mg/kg given rapidly over several minutes do not produce any observable side or toxic effects.³⁹ We consider this as supportive evidence that there is no significant mAb *in vivo* cross reactivity with endogenous ligands that affect normal physiological functions.

The size of the administered dose of an antibody is another safety consideration. For new antibody therapies to be successful, the necessary doses must at least be consistent with other, similar antibody therapies. The cancer mAb therapies, rituximab and cetuximab, are given in doses of 375 and 400 mg/m² — or total doses approaching 1 gram.^{62, 63} Scaling existing rat data to human doses using species pharmacokinetic differences, it can be predicted that a single 1-g dose of the anti-PCP mAb in humans (as a chimeric or humanized mAb) could substantially reduce the adverse health effects and potential lethality of a 1.2 g/day binge of PCP use for up to 4-6 weeks.

This prediction is based on several assumptions. First, the PCP dose of 18 mg/kg/day in the rat is the human equivalent of 1.26 g of PCP per day for an average adult male 70-kg human (18 mg kg⁻¹ d⁻¹ times 70 kg = 1,260 mg/day). Second, the lowest effective dose of anti-PCP mAb in our rat studies (15 mg/kg) is equivalent to a 1 g total dose of mAb in a 70-kg human (15 mg kg⁻¹ times 70 kg = 1,050 mg). Third, the predicted duration of the mAb protective effects in humans is based on an 8 day biological half-life of murine mAb IgG in rats,⁴⁶ scaled up to the biological half-life (21–25 days) of a human IgG in humans.⁶⁴ If these scaling assumptions are correct, a human form of anti-PCP mAb6B5 would allow extended intervals between doses and would allow patients to receive single doses every 3-4 weeks, thus increasing patient compliance. We anticipate similar effects for our anti-METH mAbs as they progress through preclinical development.

Another safety consideration is the possibility that users who receive a dose of an anti-drug mAb may attempt to surmount the protective effects of the mAb with large stimulant doses. A theoretical concern is that these patients might overdose themselves after reaching a so-called threshold of antibody protective effect. An inadvertent overdose in this scenario is unlikely for at least two reasons. The first is that the user is likely limited in the amount of stimulant he can obtain, either due to drug availability or economic reasons. Second, there does not appear to be a threshold for protective antibody effect, over which an overdose occurs. In preclinical studies in rats,⁶⁵ we administered an infusion of PCP to rats at a dose that can result in death in as many as 25% of the animals. After attaining steady-state PCP concentrations, a single dose of the anti-PCP mAb was given, equal to 1/3rd mol-eq to the amount of PCP in the rat. One day later, an additional intravenous bolus of PCP (1 mg/kg) was given to the rats, in an attempt to overcome or overwhelm the effects of the antibody. None of the rats receiving the anti-PCP mAb experienced untoward effects of the additional PCP bolus dose. Indeed, their behavior was normalized compared to the untreated rats. Two of the rats that did not receive the anti-PCP mAb nearly died and had to be resuscitated.

Lastly, immunotherapies could be used to determine whether patients have used METH during the treatment (if they entered the program drug-free). METH should remain bound to the antibody for prolonged periods of time,⁶⁴ and thus METH should be detectable in the bloodstream for an extended period of time (weeks). This type of ‘immune surveillance’ could

be used to identify patients at high risk for recidivism. These patients could be given the option of more aggressive (e.g., inpatient) therapeutic regimens.

GENERATION OF NOVEL ANTI-METH ANTIBODIES

While hapten-driven selection of mAbs by hybridoma technology is still a state of the art technique for generating therapeutic mAbs, there are other methods for generating smaller fragments and for customizing affinity and specificity. One of these methods is through the use of single chain antibody fragments (scFv, singular and plural), consisting of the variable domain binding sites of the immunoglobulin heavy (V_H) and light chains (V_L). ScFv are engineered by linking the two variable domain sequences of IgG via use of a polymerase chain reaction to form a single DNA coding sequence, instead of the two coding sequences needed for cellular formation of intact IgG. A well chosen linker between the V_H and V_L domains automatically ensures the expression of the proper stoichiometry of V_H and V_L chains and stability during domain folding.^{66, 67} It is also possible to make this minimal fragment without substantively changing the affinity or specificity of the binding, although this not guaranteed. The single polypeptide sequence of the scFv does not require the complex intracellular assembly of intact IgG. Thus, the protein can be expressed in either prokaryotic or eukaryotic cell lines, at potentially lower cost production costs. Additionally, scFv sequences can be changed *in vitro* using recombinant DNA technology, an important application for refining affinity, specificity, and stability.

To test the feasibility of scFv as a short acting antagonist for METH overdose, we produced a high affinity therapeutic scFv against METH (called scFv6H4).³⁶ Anti-METH scFv6H4 was genetically engineered by designing a coding sequence that would join the V_H and V_L domains of the parent mAb6H4 with a 15 amino acid linker. The genetic re-engineering of the parent mAb into scFv6H4 changed the protein from a ~150 kDa protein with two anti-METH binding sites into much smaller ~27.4 kDa protein with one METH binding site. The resulting antibody fragment had the same affinity for METH ($K_D = 10$ nM) as the original anti-METH mAb6H4 (IgG, κ light chain, $K_D = 11$ nM) from which it was derived. It also maintained the same specificity for METH-like compounds.

To test the *in vivo* efficacy of the scFv6H4, male Sprague-Dawley rats were first implanted with subcutaneous osmotic pumps that infused 3.2 mg/kg/day of METH.³⁶ After reaching METH steady-state levels, the scFv6H4 (36.5 mg/kg, equimolar to the METH body burden) was administered. Serum pharmacokinetic analysis of METH and scFv6H4 showed that the scFv6H4 produced a 65-fold increase in the METH concentrations, along with a 12-fold increase in the serum METH area under the concentration-time curve over an 8 hr period after scFv6H4 administration. Interestingly, the scFv6H4 monomer was quickly cleared from the rats' serum (with an apparent $t_{1/2\lambda_z}$ of 5.8 min) or converted to multivalent forms. These larger scFv6H4 multivalent forms (dimers, trimers, etc.) had a $t_{1/2\lambda_z}$ of 3.8 hr, suggesting that the apparent rapid clearance of the monomeric form was in part a rearrangement to more stable multimeric forms. The significantly increased METH serum molar concentrations in the presence of anti-METH scFv6H4 correlated directly with scFv6H4 serum concentrations of these multimeric forms of the scFv, and not the monomeric form of scFv that was quickly cleared. These data suggested that the scFv6H4 multimers (and not the monomer) were responsible for the prolonged redistribution of METH into the serum.

The possibility of lower cost production and reduced antigenicity are potential advantages of using scFv as antagonists against drugs of abuse for overdose treatment. However, due to their small size, scFv are cleared rapidly from the blood stream.⁶⁸ While this pharmacokinetic property is probably advantageous for treating drug overdose, it precludes its use as a long-acting antagonist. Nevertheless, there is significant effort toward creating post-translational

modifications that could improve *in vivo* protein pharmacokinetic properties. One such technique is “PEGylation,” in which the protein surface is covalently attached to polyethylene glycol (PEG) chains. This protein PEGylation can lead to a decrease in renal clearance, reduced immunogenicity, improvements in solubility and stability, increases in the biological half-life, and reduced toxicity.^{68, 69}

CONCLUSIONS

Even though immunization for treating diseases of METH addiction is still in preclinical development, this is a rapidly evolving process. The potential medical applications for anti-METH immunotherapy are treating METH-induced acute overdose of the drug, reducing relapse METH abuse, and protecting at risk populations who are currently using the drug but are not yet dependent. It should never be used as a preventative childhood or adult protection in case a person might be exposed to the drug in the future. For treating METH overdose, passive immunotherapy with mAbs (or small molecular weight antigen binding fragments) is the only viable option, since active immunization would take too long to produce sufficient titers to be effective in an acute METH overdose. The most important and most challenging medical goal is to treat METH addiction through the chronic prevention of relapse to METH use. In this context an active vaccination might be a viable, cost effective option, especially if the abuser is willing and motivated to stay abstinent during the initial period of immunization and immunological boosting of the immune response. Anti-METH mAb treatment would not suffer from a prolonged period of waiting for anti-METH titers to rise since an infusion of the anti-METH mAb would offer immediate protection. However, the cost of mAb treatment would be significantly greater than active immunization. It might also be possible to start a course of mAb therapy, while waiting for the titers to rise as part of an active immunization, or when titers begin to decline from active immunization. However, the immunological safety of combined passive and active immunotherapy would have to be rigorously tested for safety. Regardless of which immunotherapy is used, a course of treatment of 6-24 months of this anti-METH protective therapy may be necessary to allow adequate recover from the strong cravings and to overcome possible relapses to METH use. Since METH craving can be spontaneous and overwhelmingly strong, the most promising treatment approach to prevent relapse to METH taking is a combination of active or passive immunization along with cognitive behavioral intervention.

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Abbreviations

CNS, central nervous system
DA, dopamine
5HT, serotonin
NE, norepinephrine
GABA, gamma aminobutyric acid
CVS, cardiovascular system
Fab, antigen-binding fragment
IgG, immunoglobulin G
K_D, dissociation constant
KLH, keyhole limpet hemocyanin
mAb, monoclonal antibody
METH, (+)-methamphetamine

PEG, polyethylene glycerol
 PCP, phencyclidine
 scFV, single chain antibody fragment
 V_L, immunoglobulin variable light chain fragment
 V_H, immunoglobulin variable heavy chain fragment

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Figure 1.

Upper panel: METH effects in the brain, BEFORE anti-METH antibody treatment. After taking METH (circles), the drug is delivered to the brain through the blood stream (left barrel) where the drug rapidly penetrates the blood brain barrier (①, dashed line). In the brain, METH interacts with the dopamine transporter, monoamine oxidase, and vesicular transport mechanisms (②), causing CNS-related effects of METH (③). Because of the concentration gradient of METH across the blood brain barrier, more METH initially enters the brain (“in” arrow) than is removed (“out” arrow).

Lower Panel: METH effects in the brain, AFTER anti-METH antibody treatment.

In the presence of anti-METH antibodies (Y-shaped objects), METH is no longer able to freely move across the blood brain barrier, due to high affinity binding to the antibody. Thus, a much smaller amount of METH is able to penetrate the blood brain barrier (①, dashed line). Due to this altered drug concentration gradient, METH leaves the brain (“out” arrow) at a relatively higher rate than it enters. This results in a cascade of significantly reduced amounts, and rates of association, of METH at the sites of action within CNS nerve terminals (②, compare K_{on} and K_{off} arrows at nerve terminals before and after antibody treatment). Antibody binding of METH leads to significantly attenuated CNS (③) and peripheral effects, symbolized by the smaller arrows for CNS and peripheral effects in the lower panel.

Table 1**Complications of Methamphetamine Use**

Acute Complications	Chronic Complications
<ul style="list-style-type: none"> • Hypertension, tachycardia dysrhythmias leading to myocardial infarction and sudden cardiac death • Cerebral hemorrhage and edema, stroke, seizures leading to permanent brain injury and death • Acute psychosis leading to violence, aggression, injury to the patient and others • Hyperthermia, electrolyte disturbances leading to rhabdomyolysis and acute renal failure 	<ul style="list-style-type: none"> • Chronic hypertension, coronary artery disease, cardiomyopathy, myocarditis, and cardiac valve disease • Chronic psychosis, paranoia, hallucinations, delirium, which can be similar to schizophrenia • Long-term neurotoxicity, ranging from short-term memory loss to permanent neuropsychiatric consequences • General debilitation and increased vulnerability to infectious diseases, e.g., human immunodeficiency virus (HIV)

For review see refs. 3, 5, 6, 50, 70-72