EXPERT REVIEW OF VACCINES
https://doi.org/10.1080/14760584.2020.1857738

Taylor & Francis
Taylor & Francis Group

REVIEW

Vaccine development against methamphetamine drug addiction

Md Kamal Hossain, Majid Hassanzadeganroudsari, Kulmira Nurgali and Vasso Apostolopoulos

Institute for Health and Sport, Victoria University, Melbourne, VIC, Australia

ABSTRACT

Introduction: There are currently no effective treatments for Methamphetamine (METH) addiction and psychotherapy remains the sole treatment option. The development of immunopharmacotherapies for the treatment of drug addiction, overdose, and relapse management appears to be promising alternative and a significant body of information has been generated using various vaccine development strategies. Herein, we present an update on the developments toward anti-METH vaccines and their study outcomes in preclinical and clinical studies.

Areas covered: The scope of this article is to present an update on METH vaccine development strategies such as active vaccination through hapten design and the passive immunization through monoclonal antibodies along with preclinical and clinical studies. The relevant literatures and clinical trial outcomes were searched in databases including Google, Google Scholar, PubMed, Science Direct, ClinicalTrials.gov, and www.anzctr.org.au using specific keywords.

Expert opinion: Significant improvements have been developed for immunopharmacotherapies for METH addiction over the last two decades. However, only one monoclonal antibody candidate has been evaluated in a phase I clinical trial. At this moment, it is essential to evaluate the safety and efficacy of potential candidates in clinical trials to validate the importance of this platform drug-vaccine conjugation in order to manage or overcome METH addiction.

ARTICLE HISTORY
Received 12 August 2020
Accepted 25 November 2020

KEYWORDS
Methamphetamine; ice; METH; addiction; vaccine; hapten; meth conjugate; immunotherapy; antigen delivery; immune responses

1. Introduction

Methamphetamine addiction is a complex and dynamic public health issue affecting approximately 24 million users globally [1]. Over sixty percent of the global METH users are located in South East Asia and Oceania [1]. In the United States, approximately 1.6 million people have used METH [2] and in Australia, 280,000 people have used METH in the past year [3]. Long-term abuse of METH is associated with numerous health risks which include addiction, violent behavior, paranoia, risk of contracting HIV and hepatitis, severe 'METH mouth', and intense itching and skin sores from scratching [4]. In the case of discontinuation of METH use, withdrawal symptoms include intense drug cravings, severe depression, anxiety, fatigue, and psychosis. METH use can also cause significant social problems including domestic and social violence, crime, homelessness, unemployment, and imprisonment [5].

METH is a highly addictive stimulant. Current management methods to reduce METH addiction and prevent relapse are ineffective in controlling this complex and growing public health concern [6]. Despite tremendous efforts in the last few decades, there are no effective treatment options for METH addiction. Currently available treatments for METH addiction mainly involve psychotherapy including cognitive behavioral therapy, contingency management, residential rehabilitation, 12-step facilitation, and relapse prevention programs [1,6,7]. The limitations and inefficiency of current treatment methods necessitate the development of alternatives such as anti-METH vaccines for METH addiction [8]. Developing a vaccine for METH will provide a complementary strategy for existing therapies. The mechanism of anti-METH vaccines is different from conventional pharmacological treatments. An anti-METH vaccine will not act as an antagonist for the drug binding site in the brain; rather, the antibodies generated in response to the METH vaccine will work by changing the concentration of METH distribution in the brain [8,9]. Vaccine or immunotherapy provides other opportunities in the treatment of drug addiction; immunotherapy against cocaine and nicotine has already reached human clinical trials [10–13]. However, the progress of vaccine development against METH addiction has not been evaluated comprehensively. One monoclonal antibody (mAb) for METH addiction reached Phase I clinical trial [14,15]. Development of improved strategies to prevent drug use or, the development of new improved treatments against METH addiction is a National Institute on Drug Abuse (National Institute of Health, USA) priority [16]. As such, information regarding vaccine developments and methodologies against METH addiction is evolving rapidly. A number of studies have reported the development of mAb and a series of METH-conjugated vaccines through structural modification of METH, which is commonly known as 'hapten design' [8,14,17–22]. Researchers are continuously adopting cutting edge technology to develop a successful anti-METH vaccine. In this review, the METH vaccine development strategies have been reviewed along with clinical and non-clinical outcomes to provide a broad picture to the reader along with new insights and future directions. Fresh insights have been generated on

CONTACT Vasso Apostolopoulos vasso.apostolopoulos@vu.edu.au Institute for Health and Sport, Victoria University, Melbourne, VIC, Australia

Article highlights

- Immunotherapy for the treatment of METH addiction has great potential and significant developments have been made in this area.
- Anti-METH vaccine development using 'Hapten Design' appeared to be very promising and draw the attention of scientific community.
- Active and passive immunization techniques for METH vaccine have demonstrated promising results in preclinical stages.
- New potential vaccine development strategies for drugs of abuse are emerging very fast and will revolutionize the METH vaccine development platform.
- Funding will play an important role in the assessment of the METH vaccine candidates in clinical trial phases.
- Multiple candidate vaccines have demonstrated encouraging results in preclinical stages.

emerging vaccine development strategies and are already being investigated for various drugs of abuse, excluding METH. These are now suggested for consideration in the development of a METH vaccine.

2. Methodology

Searches were conducted using the databases Google, Google Scholar, PubMed, Science Direct, clinicalTrial.gov, and www.anzctr.org.au to identify the articles and clinical trials related to METH addiction and vaccine development strategies. The keywords used were methamphetamine, methamphetamine addiction, methamphetamine AND treatment, methamphetamine addiction AND monoclonal antibodies, methamphetamine AND vaccine, methamphetamine addiction AND conjugated vaccine, methamphetamine AND hapten design, Methamphetamine AND nano-vaccine, strategies for methamphetamine vaccine. All the above were repeated by replacing methamphetamine with METH OR ice. The selected publications include the vaccine development studies, preclinical or clinical trial reports that were conducted irrespective of their publication year. In order to gain updated information regarding ongoing efforts on clinical trials, we searched the ClinicalTrials.gov and Australia-New Zealand clinical trial (www.anzctr.org.au) registry database using the terms, methamphetamine OR METH addiction AND vaccine, monoclonal antibodies AND methamphetamine OR METH, methamphetamine OR METH conjugated vaccine, methamphetamine OR METH addiction and immunotherapy, as keywords.

The summary and title of the obtained articles were assessed by the authors and classified as included or excluded. The studies related to METH vaccine development, clinical and non-clinical data, and new concepts for METH vaccine development were included and the studies that did not mention METH AND vaccine were excluded from further analysis. Articles that were not written in English were excluded from the study. The overall article selection procedure is presented in Figure 1.

3. Approaches for METH vaccine development

In general, the immunization process can be categorized into two groups: active and passive immunization. A specific antibody can be produced in a patient's body by both approaches [23]. In an active vaccination process, anti-drug vaccines are injected into patients to produce specific anti-drug polyclonal antibodies [24,25]. In the passive vaccination process, B cells which secrete anti-drug polyclonal antibodies are isolated and fused with myeloma cells, and after 2–3 rounds of screening (specificity to anti-METH) and cloning, monoclonal antibodies (mAb) are obtained. The cloned and identified mAbs usually those with the highest affinity and specificity are taken through complex genetic engineering processes either from animals or antibody libraries and humanization of the chimera by selectively altering the amino acid sequence to retain the original specificity (Figure 2) [24,26]. The developed anti-drug mAb is injected into a patient's body to fight against the drug. Both approaches have been evaluated for the treatment of METH addiction in mice, rats, and rodents and have been shown to be effective in animal models [27,28]. However, lately the active immunization approach using drug-like antigens conjugated to an immunogenic carrier protein has received much attention for its ability to modify the structure of METH and produce higher antibody levels, which is a key criterion for a successful vaccine. Updates on the development strategies for both approaches, along with preclinical and clinical studies, have been summarized in the following sections.

3.1. Active immunization approach through hapten-carrier design

The conjugate vaccines development strategies through hapten design have been studied most extensively for all the drugs of abuse including METH [8,9]. METH is a small molecule and the body's immune system cannot recognize it. Therefore, METH or METH with a linker (hapten) needs to be tagged with a known immunogenic carrier to be recognized by the immune system and its effective processing (Figure 2) [8,29]. This strategy has been shown to be effective for both nicotine and cocaine vaccines and the strategy is viable for the application of developing a vaccine against METH [8]. In order to prevent METH from entering the central nervous system (CNS), a high concentration of anti-METH antibodies is required. The selectivity and affinity of the anti-METH antibody largely depend on an effective METH hapten molecule. This is a significant challenge as METH is a small molecule with limited chemical epitope [8,20]. Inclusion of a linker at the appropriate position of the 'hapten' (METH) is crucial for the generation of high antibody titers and antibody specificity [30]. Hence, the proper design of hapten is important for immune recognition due to its role in the presentation of target antigen to the antigen presenting cell. A series of METH haptens have been investigated (Table 1) by various research groups in the last few decades in regards to their efforts to develop a METH vaccine (hapten-carrier approach).

One of the first examples of METH hapten design and conjugation to protein has been reported in 1973 by Cheng et al. [31]. The hapten N-(4-aminobutyl) methamphetamine was developed and conjugated with bovine serum albumin (BSA) for the validation of a radioimmunoassay method. A Korean research group has used the same hapten-BSA conjugate along with other carrier proteins to detect METH in urine samples [32–34]. The first vaccine intended for the application in humans was assessed by a research team at

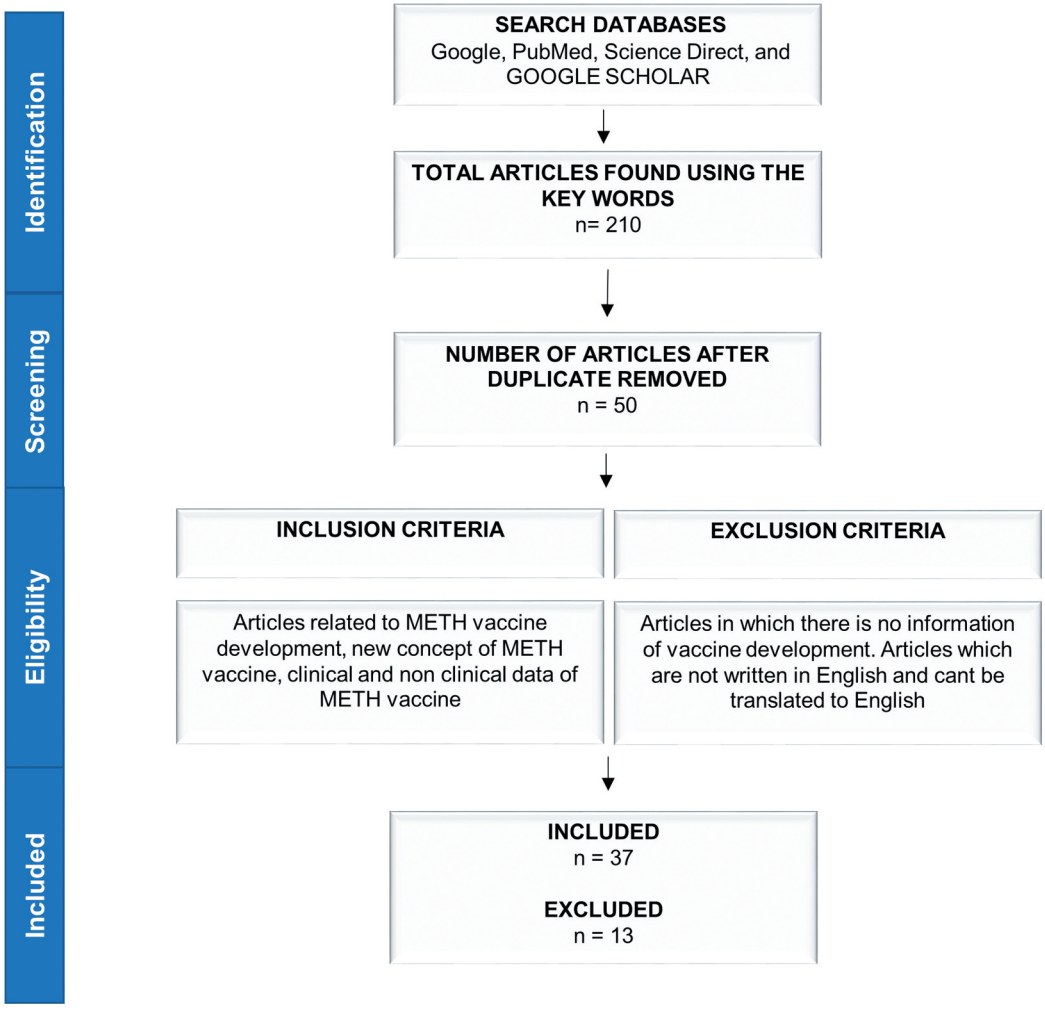

Figure 1. Overall procedure of article selection for this review.

the University of Arkansas in 2001 [17]. They developed a METH haptenic compound by introducing 6-carbon spacers linked at the para position of the phenyl ring and then conjugated with keyhole limpet hemocyanin (KLH) carrier to assess their effectiveness in a rat model. The immunized rats were repeatedly injected with 3 mg/kg METH twice a week. They demonstrated that the antibody levels were not interrupted when METH was administered repeatedly. Later on, the same group generated mAb and were tested in a rat model with success. A study by Moreno et al. reported seven haptens and investigated their ability to produce antibodies in mice [20]. In that study, the investigators were able to design seven haptens mainly using Alkylating sulfhydryl linkers. Six haptens were investigated for their ability to mount an antibody response in mice and determined the ability of the antibodies to bind to METH and amphetamine *in vitro*. Three hapten derivatives, MH2(R), MH6, and MH7, were able to generate strong anti-METH antibody titers. Strategic molecular constraints and stereo-chemical requirements were crucial to generate even higher antibody titers using MH2(R). MH2(R), MH6, and MH7 were able to generate moderate antibodies for both METH and amphetamine (AMP) [20]. However, MH6 hapten was taken further due to its higher antibody titer and its effective binding specificity toward METH. The affinity of MH6 for (+) METH was 130 nM and 169 nM for MH7. In a more recent study, researchers at The Scripps Research Institute have demonstrated that methyl-linked METH hapten (S)MLMH-TT adjuvanted with CpG ODN 1826 and alum produced anti-METH antibodies in high titers and have reduced (+)-METH distribution to the brain [35]. The researchers concluded that the inclusion of (S)-stereochemistry in METH hapten is very crucial to ensure optimal protection.

Most of the reported earlier studies predominantly focused on the hapten design, its specificity, and antibody production capacity. Subsequently, the focus was shifted toward assessment of active vaccination on METH-induced animal behaviors [36]. As such, the Janda group at The Scripps Research Institute demonstrated that METH haptenic derivatives MH6 was successful in reducing the METH-induced locomotor and thermoregulatory effects [21]. The vaccine comprised the conjugate MH6 with KLH and the Sigma adjuvant system (SAS®) – a stable oil-in-water emulsion adjuvant used as an alternative to the classical Freund's water-in-oil emulsion [21]. MH6-KLH-SAS was able to generate higher Abs titers in the range of 1:70,000–1:80,000 in rats which were maintained for 3 weeks. In the same study selectivity of MH6 antibodies to bind to AMP, METH, 4-methyl-N-methylcathinone

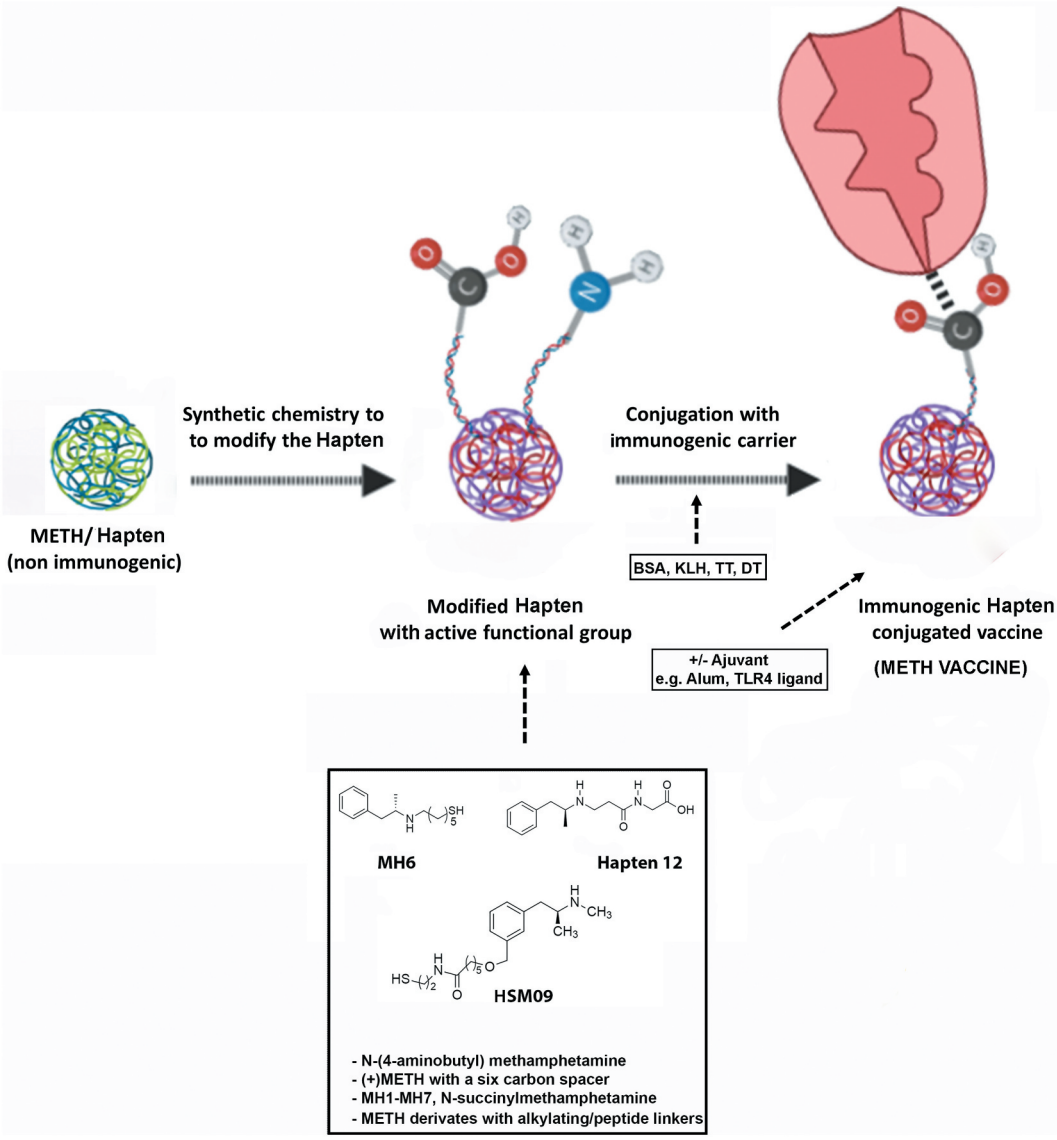

Figure 2. Schematic diagram of methamphetamine (METH) conjugate vaccine development through hapten design, (BSA, bovine serum albumin; DT, diphtheria toxoid; KLH, keyhole limpet hemocyanin; TT, tetanus toxoid). Chemical structures of some of the encouraging METH haptens (MH6 [20], Hapten 12 [8], HSM09 [38]).

(4-MMC), or methylenedioxy-methamphetamine (MDMA) were evaluated by equilibrium dialysis. The MH6 antibodies demonstrated excellent affinity and specificity for METH and AMP [21]. It was also reported that METH concentration was greater in serum than CNS following acute METH injection in vaccinated rats. These findings support the idea that MH6 METH hapten could be a potential candidate to prevent METH addiction. Recently, the researchers at The Scripps Research Institute further investigated the effect of MH6-KLH in female rats [37]. The idea behind this study was to discover the effects of sex on the development of METH specific antibody and their subsequent effects on behavioral and physiological end points. In that study, female Wistar rats were vaccinated by MH6-KLH and exposed to METH via vapor inhalation at the dose rate of 1000 mg/mL in propylene glycol and then 0.25 to 1 mg/kg intraperitoneal injection. MH6-KLH was successful to reduce the locomotor activity caused by 0.25 mg/kg METH, intraperitoneal. So far haptenic derivatives have shown great promise when conjugated with various carrier proteins and could be suitable candidates for clinical trials. A list of some successful haptenic derivatives are included in Figure 2 with their structures.

In another study, a vaccine was developed by conjugating a hapten SM09 with KLH which was able to prevent the rats from METH-induced impairment of food responses [38]. Initially rats were vaccinated by KLH-SM09 and then both control and vaccinated rats were injected by METH at the dose of 0.3 to 3.0 mg/kg. The control group demonstrated reduced food intake even at the dose of 3 mg/kg whereas the vaccinated rats showed no alterations in food-induced behavior at all the METH dosages. It was concluded that KLH-SM09 conjugated vaccine was effective to reduce METH-induced adverse effects. Another haptenic derivative of METH, N-succinylmethamphetamine (SMA), was developed by the Orson group at the VA Medical Center in Houston, TX, and assessed its effect on animal models by conjugating with KLH (SMA-KLH) [29]. SMA-KLH was successful in reducing the METH-induced hyper locomotion in mice. Considering KLH is not approved for human use, the same research group later used

Table 1. Summary of preclinical studies using various METH hapten derivatives and carrier protein.

Hapten derivatives	Carrier protein	Study outcome	Model Tested	Reference
N-(4-aminobutyl) methamphetamine	Bovine Serum Albumin (BSA)	Validation of a radioimmunoassay method	Mice	[31]
(+)METH with a six carbon spacer group at the para position of the ring structure	keyhole limpet hemocyanin (KLH)	Rats immunized with METH hapten-KLH conjugate developed METH antibody titers	Sprague–Dawley rats	[17]
MH1-MH7	KLH	MH2, MH6 and MH7 demonstrated very promising anti-METH antibody titer and METH affinity	GIX Mice	[20]
MH6	KLH	MH6 was successful in reducing the METH induced locomotor and thermoregulatory effects	Rats	[21]
SMO9	KLH	SM09 with KLH was successful in preventing the rats from METH-induced impairment of food responses	Rats	[38]
N-succinylmethamphetamine (SMA)	KLH and Tetanus Toxoid (TT)	SMA-KLH/TT was successful in reducing the METH induced hyper locomotion in mice model	Mice	[39]
Nine (9) METH hapten derivatives with alkylating and peptide linkers	TT and Diphtheria Toxoid (DT)	Hapter 12 (12-TT) conjugated with TT & alum/CpG ODN 1826 as adjuvant demonstrated excellent antibody titer (300,000) and was able to reduce METH induced locomotor activity compare to control group	Webster mice	[8]
MH6	KLH	MH6-KLH was successful in reducing the locomotor activity caused by 0.25 mg/kg METH, intraperitoneal	Female Wistar rats	[37]

the same hapten, SMA, and conjugated it to tetanus toxoid (TT); an approved carrier for use in humans [39]. In order to increase the immunogenicity of SMA-TT, aluminum hydroxide was added to the formulation as an adjuvant [39]. Mice were vaccinated with SMA-TT at weeks 0 and 3. Initially mice in both vaccinated and control groups were conditioned with 0.5 mg/kg and 2 mg/kg METH. Then a second dose of METH was given to evaluate METH levels in the brain. It was concluded that the METH specific antibodies were elevated at week 8 and remained stable up to week 12 [39]. The vaccine was effective in reducing the entry of METH to the CNS at both doses. Very recently, the same research group further investigated the SMA-TT conjugate along with a toll-like receptor-4 (TLR4) synthetic agonist, E6020, in mice [40]. SMA-TT-aluminum hydroxide vaccine plus E6020 demonstrated greater affinity and threefold higher antibody titers compared to formulations without E6020. The vaccine formulation with E6020 significantly reduced the penetration of METH to the brain [39].

In another study, nine haptenic compounds using mainly alkylating linkers were studied [8]. One out of nine was designed by using peptide linker (BOC-Gly-Gly-OH). Amphetamine was used as starting material for the design of most of the haptenic compounds in their study due to the ease of modifying the primary amine groups on it. The developed METH hapten derivatives were conjugated to TT or diphtheria toxoid (DT) and evaluated their effectiveness in producing METH specific antibody responses and also their ability to reduce METH-induced locomotor activity in animal models. Among all the haptens conjugated with DT or TT, hapten 12 conjugated with TT (12-TT) and mixed with aluminum hydroxide and TLR9 agonist (CpG ODN1826) induced excellent antibody titer (1:300,000) and was able to reduce METH-induced locomotor activity compared to a control group when METH was injected at the dose of 0.5, 1, 2, 4 mg/kg bodyweight [8]. In that study, it was concluded that secondary amine in METH is crucial for high affinity antibody production; a peptide-based linker was more efficient in eliciting the antibody production; and TT was able to produce higher antibody due to the higher lysine residue on its structure.

A search was conducted at the ClinicalTrials.gov online registry, for anti-METH vaccines in human clinical studies, and no studies were registered for the assessment of such vaccines (accessed online on 26/03/2020). There were significant developments in the design of conjugated METH vaccines and their assessment in terms of selectivity, antibody production capacity, and modulation of METH-induced animal behavior in the last two decades. However, no study was translated into human clinical trials. METH conjugated vaccines have shown promise in pre-clinical models and efforts should be aimed at translating pre-clinical findings to human clinical trials in METH addicted individuals. There is a desperate worldwide need for an effective treatment modality to control METH addiction and its associated complications. It deserves urgent, desperate initiatives in order to succeed.

3.2. Passive immunization

Passive immunization is the process of administering a pre-generated, well-defined, well-characterized purified antibody [15,41]. Traditionally, the anti-METH antibodies for passive immunization were produced by immunizing animals with an immunogenic hapten-carrier complex [41]. Then purified and well-characterized humanized or human mAbs were administered to the patients to prevent the effect of drugs. Polyclonal antibodies in active immunization process are produced by different B cell clones in the body's immune system which are able to bind to a number of different epitopes of the antigen. On the contrary, mAbs have monovalent affinity and can only recognize the same epitope (or one epitope) of the respective antigen. The synthesis of monoclonal(mAb) anti-drug antibodies involves complex and time-consuming genetic engineering processes [42]. The vaccine development processes for both active and passive immunization approaches share common steps up to the development of an immunogenic METH-linker-protein carrier. The

development of mAbs has additional steps that involve complex genetic engineering processes. A schematic diagram of mAb development in mouse and chimeric mouse/human mAb is shown in Figure 3.

There are number of technologies for the development of mAbs for therapeutic application such as chimeric mAbs which is 70% human, Phage display for humanized mAb, transgenic mouse for human mAb, and Single B cells for human mAb [43]. The later technologies are getting increased attention due to the ease of production of highly specific, sensitive, and less immunogenic mAbs and number of approved mAb are increasing from these newer technologies and could be explored for anti-METH mAb. Although chimeric mAbs are 70% human, still it is too immunogenic and required further modification for humanization. On the other hand a humanized antibody demonstrated lower immunogenicity, efficiently activate the human effector functions to take place; and the serum half-life of the humanized mAb is significantly higher than mouse/chimeric mAbs [44,45]. Every type of mAbs development technologies have their own challenges and the common one is the requirement of sophisticated technology.

Despite the complex manufacturing process, mAbs have been explored for the control of METH-induced addiction in animal models (Table 2). Passive immunization through mAbs for the management of METH overdose toxicities has a number of advantages [28,42,46]. Firstly, the onset of action of mAbs is very quick and can bind with METH immediately compared to active vaccination, which is particularly important for the treatment of METH overdose. Secondly, METH mAbs are highly specific to METH and do not react with other endogenous molecules and hence, have low CNS side effects. Thirdly, METH mAbs have high affinity. Lastly, mAbs acts through a unique mechanism by which they combine with METH in the bloodstream and reduce the penetration of METH to the CNS, and could be safely co-administered with

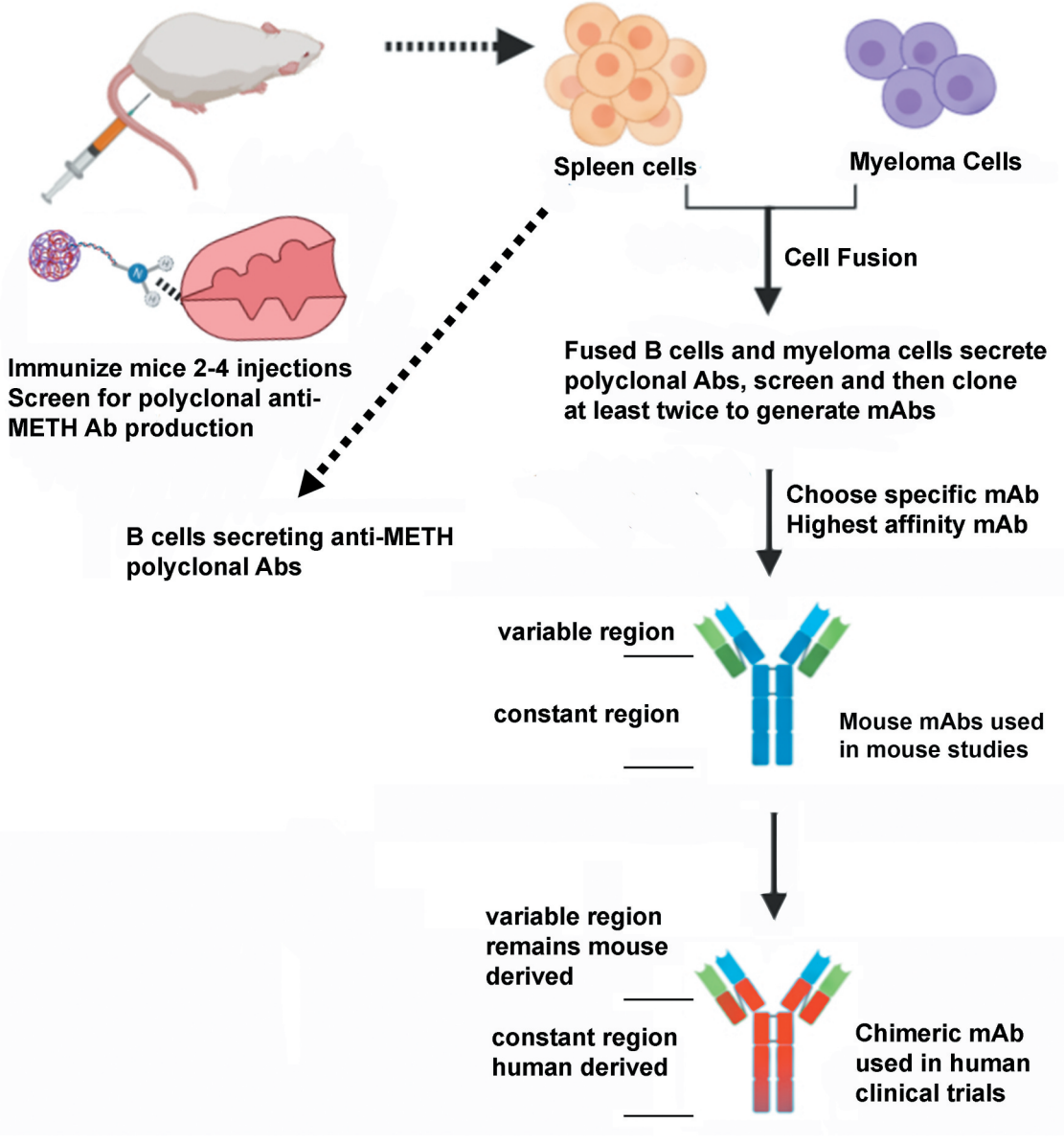

Figure 3. Schematic diagram on the production of mouse monoclonal antibody using animal model. Mouse/human chimeric antibody shown.

Table 2. Summary of preclinical and clinical studies using various anti-METH mouse monoclonal antibodies (mAbs) or human/mouse chimeric mAbs.

Vaccine description	Study outcome	Model Tested	References
Two anti-METH mAbs with different affinity	mAbs with higher affinity were more effective to reduce the locomotor activity	Rats	[17]
Anti-(+)-METH mAbs (mAb; KD = 11 nM)	Rats treated with anti-METH-mAbs treated showed a reduction of METH concentration of > 60%t for brain and an increase of METH concentration greater than 6,600% for serum	Sprague–Dawley rats	[28]
Two murine derived anti-METH mAbs (mAbH4 & mAbH8)	Both mAbs are able to bind with self-administered METH before they enter into CNS and thus, prevents reinforcing effects and proposed these mAbs could be potential pharmacokinetic antagonist of (+)METH	Rats	[48]
Combination of anti-METH and anti-phencyclidine (PCP) mAbs	Both the mAbs demonstrated excellent drug specific selectivity and each mAbs blocked the behavioral effects of the respective drugs	Pigeons	[49]
Human-mouse chimeric mAb for (+) METH with high selectivity and affinity	ch-mAb7F9 binds with METH efficiently; ch-mAb7F9 can alter the disposition of METH, reduce volume of distribution and enhance the clearance of METH from the body significantly	Rats	[14]
ch-mAb7F9	This study finding successfully demonstrated that ch-mAb7F9 can partially attenuate some addiction-related effects of acute METH dose in an intracranial self-stimulation model	Rats	[15]
ch-mAb7F9	Phase 1 clinical trial has been conducted to assess the safety of ch-mAb7F9 in human	Humans	NCT01603147

other small molecules which mainly work in CNS for antagonistic effect [28].

A series of preclinical studies have been conducted to assess METH mAbs in terms of their affinity, selectivity, and ability to decrease METH stimulated locomotor activity. Preclinical studies have shown that this approach has potential for the management of METH overdose toxicity and the prevention of relapse. The Owens group from the University of Arkansas investigated a series of studies on anti-METH mAbs in a rat model. In a study to simulate a human treatment scenario for METH overdose, rats were injected with 1 mg/kg METH and anti-METH mAbs were given 30 minutes after METH administration. Anti-METH mAbs were successful to antagonize the locomotor activity [28]. In that study, two anti-METH mAbs with different affinities were investigated and the mAb with the highest affinity was more effective to reduce the locomotor activity [28].

In another study, the Owens group investigated the roles of anti-(+)-METH mAbs (mAb; KD = 11 nM) on (+) METH and (+) AMP serum and tissue disposition in rats [47]. The rats were pre-treated with a buffer solution (control group) or with anti-(+) METH mAbs. The following day, both groups were treated with a dose of 1 mg/kg (+) METH intravenously. Rats treated with anti-METH-mAbs showed a reduction of METH concentration of greater than 60% for brain and an increase of METH concentration greater than 6,600% for serum. The anti-METH mAbs did not show any significant cross-reactivity for AMP, suggesting that it has greater affinity for METH and efficiently reduces the penetration of the drug into the CNS. The Owens group further investigated the effect of two murine derived anti-METH mAbs on self-administration of METH in rat models [48]. These two mAbs were mAb6H8 with lower affinity and mAb6H4 with higher affinity. The rats were injected with METH at the dose rate of 0.01, 0.03, and 0.06 mg/kg (+) METH one day before the self-administration period. Both mAbs had minimal effect on the rate of self-administration of METH against the dose rate of 0.01 mg/kg (+) METH out of three dosages tested. Although mAbH4 had 20X more affinity than mAbH8, they demonstrated similar antagonism against METH. The investigators concluded that both mAbs are able to bind with self-administered METH before they enter the CNS and thus prevented a reinforcing effect, and proposed these mAbs could be potential pharmacokinetic antagonists of (+) METH.

The Owens group conducted another study using a combination of anti-METH and anti-phencyclidine (PCP) mAbs in pigeons. This was the first ever study where investigators used two drugs at the same time. These antibodies were derived from mice and tested to determine whether anti-METH and anti-PCP mAbs could prevent the discriminative behavioral effects of the drugs. Both the mAbs demonstrated excellent drug-specific selectivity and each mAbs blocked the behavioral effects of the respective drugs [49]. Later on, the Owens group designed a human-mouse chimeric mAb for (+) METH with high selectivity and affinity [14]. This antibody was able to bind with its target molecules METH, AMP, and 3, 4-methylenedioxy-N-methylamphetamine with high affinity. In this study, the investigators concluded that ch-mAb7F9 binds with METH efficiently; ch-mAb7F9 can alter the disposition of METH, reduce volume of distribution and enhance the clearance of METH from the body significantly. The findings of this study suggested to have profound therapeutic impact regarding effective doses of ch-mAb7F9 against METH, duration of action, and safety profile of ch-mAb7F9 in METH users at the time of taking METH while on ch-mAb7F9 treatment. By far this is the most successful mAb for the management of METH addiction. This preclinical study has generated a substantial body of information on the efficacy and safety of ch-mAb7F9 for the management of METH addiction and has supported the rationality of initiating clinical studies.

In yet another study by the Owens group the effects of ch-mAb7F9 were evaluated on intracranial self-stimulation following acute METH administration in rats [15]. Rats were pre-treated with mAb7F9 at the dose rate of 30, 100, or 200 mg/kg. Rats pre-treated with 200 mg/kg mAb7F9 prevented the ability of an initial injection of 0.3 mg/kg METH to decrease baseline intracranial self-stimulation thresholds, but were less efficient in reducing the effect of subsequent daily injections of METH. MAb7F9 at the dose of 200 mg/kg also generated a little but noticeable reduction in the ability of 0.3 mg/kg METH to reverse METH withdrawal-induced elevations in intracranial self-stimulation thresholds. This study finding successfully demonstrated that ch-mAb7F9 can partially attenuate some addiction-related effects of acute METH dose in an intracranial self-stimulation model, and further justifies the therapeutical potential of ch-mAb7F9 for the management of METH

addiction. In addition, ch-mAb7F9 has entered into phase 1 human clinical trial (NCT01603147; clinicalTrials.gov portal; accessed 31/03/2020) with title of 'The safety of ch-mAb7F9 for Methamphetamine Abuse'. According to Clinical Trials database, recruitment for the study was completed in 2012 and the Phase 1 study has been completed in 2014. No study results were posted on the ClinicalTrials.gov website. However, the study outcomes have been published [50]. This study was a phase 1, randomized double-blind study with a primary aim to assess the safety and tolerability of a single administration of ch-mAb7. Forty-two healthy volunteers were recruited for this study and administered ch-mAb7F9 over a range of 0.2 to 20 mg/kg bodyweight and monitored for 147 days. No dose-related potential adverse effects or discontinuation of the study by the volunteers were reported. Four out of 32 volunteers were confirmed to have anti-ch mAb7F9 at the end of the study. However, this antibody response was not dose related [50].

There has been significant progress in the design and development of mAbs for the treatment of METH addiction in recent decades. There is a substantial body of preclinical information on affinity, specificity, safety, and efficacy of newly developed mAbs which were mainly developed through hybridoma technology which eventually supported the initiation of clinical trials. Despite significant developments, only one study entered Phase 1 clinical trial using ch-mAb7F9. Again, like vaccine development through hapten design, anti-METH mAbs are mostly stuck in the preclinical stage and require a push/funding stimulus to take them to the clinical phase in order to have any chance of succeeding. As stated earlier, development of mAbs for human application is tedious, time consuming, and expensive which may be a great hindrance to the success of the approach. In contrast, conjugated METH vaccine development through hapten design offers more flexibility, is quicker to develop, and is less tedious. For these reasons efforts into this approach have been of focus, especially the researchers from the Scripps Research Institute, who conducted series of studies and generated substantial preclinical data. Sadly, there is no current candidate in clinical trial of a vaccine developed through the hapten design approach. This is mainly due to the shortage of funding and appropriate legislation, according to experts.

However, METH addiction is a serious and growing problem across the globe. There is a pressing need for an effective treatment and the beneficial aspects of a successful vaccine whether active or passive, must surely outweigh the cost involved in the design, development, preclinical and clinical trials. Therefore, funding should be readily available to ensure the success of this promising approach, and eventually for the greater benefit of mankind.

4. Conclusions

Although enormous efforts have been made to develop an effective vaccine for METH addiction, they have so far been unsuccessful. Some of the study outcomes, including active and passive immunization approaches, demonstrated promising results in preclinical studies which may be translated into clinical trials in the future. Some new vaccine development strategies are very promising and may enhance the vaccine development process. METH addiction is a complex central nervous system disease and poses a global threat. The success of the development of a METH vaccine will largely depend on the funding support and appropriate legislation to encourage the research institutions and industries to engage in this innovative and important project.

5. Expert opinion

There is a pressing need for an effective treatment for the management of METH addiction and associated complications. Immunotherapy can play a pivotal rule in the prevention of relapse due to its immune-propylaxis properties. METH-conjugated vaccine developments through hapten design are trending now. Significant developments have been achieved based on conjugated vaccine development strategies and mAbs in animal models. However, only one anti-METH chimeric mAb progressed to human clinical trial. Vaccine efficacy could be significantly different in human models compared to animal models. Level of antibody production and safety margin could also vary significantly between the models; hence, they need to be evaluated in human models for the strategies to be successful. METH vaccine studies are mostly halted at the preclinical stage and need a push to take them to the next level. The future success of the METH vaccine will depend on a number of factors which need to be addressed properly.

Some of the vaccine candidates for cocaine and nicotine were unsuccessful due to inadequate antibody responses. These clinical study outcomes offer very important message for the researchers engaged in the development of METH vaccines to harness this parameter. Of relevance, in cancer vaccine studies little antibody responses were shown with certain conjugates in animal models but in humans, high antibody levels resulted [51–53], hence, pre-clinical data do not always translate to human settings. A number of studies have been conducted to increase the antibody levels of METH vaccines in animal models. However, till now no specific benchmark on the antibody titer has been set as a reference guide which necessitates urgent human studies to set a benchmark. Currently, different studies are reporting efficacy at different antibody levels, which is confusing.

The success or failure of METH vaccines mainly depends on three components such as hapten, immunogenic carrier, and adjuvant. Over the last two decades protein-based carriers have been explored extensively as an immunogenic carrier. However, there are other immunogenic carriers such as polysaccharides which have been underexplored for METH vaccines. Emphasis should also be given to exploration of other immunogenic carriers to increase the chance of success.

Natural polymer or particle-based vaccines such as polymer particles, liposomes, VLPs, self-assembled peptides, and combinations of different materials can provide higher immunogenicity, antibody production capacity, selectivity, and efficacy due to their ability to activate the antigen presenting cells and process the vaccines efficiently compared to hapten conjugated vaccines prepared by traditional synthetic processes. The polymer or particle-based vaccine can offer accurate geometry and stoichiometry of vaccine components, and controlled hapten density. Protein carriers due to their fixed tertiary structure have a limited number of

functional groups on their surface and so are only able to bind to a limited number of haptens. In contrast, particles or polymers have higher numbers of surface functional groups and can be easily modified to add more functional groups, so that they present potential alternatives. Additionally, particle-based vaccines are able to offer focused delivery of immune modifiers and other adjuvants and can work as depots for sustained release of the vaccine at the cell surface. Particle-based vaccines have shown promising results for nicotine, heroin, and cocaine vaccines. They have not as yet been explored for METH vaccine. These newer strategies should now be focused on production of a successful vaccine for METH addiction.

Some experts believe funding is becoming increasingly critical for promotion of development studies and for clinical trials for the vaccines for substances of abuse. It has also been claimed that if there was sufficient funding, taking vaccines to clinical trials would not be a problem. Pharmaceutical industries are not willing to invest in research into addiction treatments, because they see little potential market viability. This hesitation may be due to a lack of clear guidelines or legislation on the marketing of these vaccines to the customer once they are approved. The logistics for the treatment of METH addiction are complicated and government has a role to play here. Therefore, governments need to become involved in supporting the research studies financially. Governments should also introduce appropriate legislation in terms of the marketing of these vaccines once they are approved, as a show of confidence to the research institutions.

Acknowledgments

The authors would like to thank Graeme Wise and Angelina Wise, whose generous philanthropic support made possible the preparation of this paper. The authors would also like to thank the Immunology and Translational Research Group and the Intestinal Neuropathy Group for their significant contribution. The Mechanisms and Interventions in Health and Disease Program within the Institute for Health and Sport, Victoria University Australia are also appreciated for their support. M.H. is supported by Graeme and Angelina Wise, and Md. K.H. was supported by the Victoria University Postgraduate Scholarship and the Vice-Chancellors top-up Scholarship Award.

Author contributions

All authors contributed to the conceptualization and design of the article. Md K Hossain and M Hassanzagedanroudsari wrote the article. V Apostolopoulos edited the article. Md K Hossain, M Hassanzagedanroudsari, K Nurgali, and V Apostolopooulos contributed to the interpretation of the results and helped draft or revise the manuscript. All authors have read, reviewed, and approved the final paper.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

The authors declare no conflicts of interest with respect to the authorship and publication of this article.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Md Kamal Hossain http://orcid.org/0000-0001-5173-8994
Majid Hassanzadeganroudsari http://orcid.org/0000-0002-3241-6444
Kulmira Nurgali http://orcid.org/0000-0002-2597-6929
Vasso Apostolopoulos http://orcid.org/0000-0001-6788-2771

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ballester J, Valentine G, Sofuoglu M. Pharmacological treatments for methamphetamine addiction: current status and future directions. Expert Rev Clin Pharmacol. 2017;10(3):305–314.
2. Jones CM. Patterns and characteristics of methamphetamine use among adults—United States, 2015–2018. MMWR. Morbidity Mortality Weekly Rep. 2020;69.
3. AIHW national drug strategy household survey 2016 key findings. Canberra, Australia; 2017.
4. Hellem TL. A review of methamphetamine dependence and withdrawal treatment: a focus on anxiety outcomes. J Subst Abuse Treat. 2016;71:16–22.
5. Mancino MJ, Gentry BW, Feldman Z, et al. Characterizing methamphetamine withdrawal in recently abstinent methamphetamine users: a pilot field study. Am J Drug Alcohol Abuse. 2011;37(2):131–136.
6. Panenka WJ, Procyshyn RM, Lecomte T, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend. 2013;129(3):167–179.
7. Radfar SR, Rawson RA. Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. Addict Health. 2014;6(3–4):146.
• **It provides very good overview on METH addiction global epidemiologic trend, associated harms, psychological impact and treatment options.**
8. Collins KC, Schlosburg JE, Bremer PT, et al. Methamphetamine vaccines: improvement through hapten design. J Med Chem. 2016;59(8):3878–3885.
•• **Provides very impressive overvies on the METH vaccine develpemnt through Hapten design and preclinical studies in mice model**
9. Bremer PT, Janda KD. Conjugate vaccine immunotherapy for substance use disorder. Pharmacol Rev. 2017;69(3):298–315.
•• **Provides comprehensive overview on conjugated vaccine development for substance of abuse including METH. It covers critical element of conjugated vaccine such as hapten structure, adjuvant types,and immunogenic carrier system**
10. Cornuz J, Zwahlen S, Jungi WF, et al. A vaccine against nicotine for smoking cessation: a randomized controlled trial. PloS One. 2008;3(6):e2547.
11. Hatsukami DK, Jorenby DE, Gonzales D, et al. Immunogenicity and smoking-cessation outcomes for a novel nicotine immunotherapeutic. Clin Pharmacol Ther. 2011;89(3):392–399.
12. Martell BA, Orson FM, Poling J, et al. Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: a randomized, double-blind, placebo-controlled efficacy trial. Arch Gen Psychiatry. 2009;66(10):1116–1123.
13. Haney M, Gunderson EW, Jiang H, et al. Cocaine-specific antibodies blunt the subjective effects of smoked cocaine in humans. Biol Psychiatry. 2010;67(1):59–65.

14. Stevens M, Tawney R, West C, et al. Preclinical characterization of an anti-methamphetamine monoclonal antibody for human use. MAbs 2014;6:547–555. PMID: 24492290.
15. Harris AC, LeSage MG, Shelley D, et al. The anti-(+)-methamphetamine monoclonal antibody mAb7F9 attenuates acute (+)-methamphetamine effects on intracranial self-stimulation in rats. PLoS One. 2015;10(3):e0138959.

•• **This mAbs based METH vaccine has demostrated excellent results in preclinical stahe and the same candidate has also been evalauted in phase I clinical**

16. National Institute on Drug Abuse (NIDA); [cited 2020 Jul 29]. Available from: https://www.nih.gov/about-nih/what-we-do/nih-almanac/national-institute-drug-abuse-nida
17. 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 Immunopharmacol. 2001;1(2):329–338.
18. Duryee MJ, Bevins RA, Reichel CM, et al. Immune responses to methamphetamine by active immunization with peptide-based, molecular adjuvant-containing vaccines. Vaccine. 2009;27(22):2981–2988.
19. Carroll FI, Blough BE, Pidaparthi RR, et al. Synthesis of mercapto-(+)-methamphetamine haptens and their use for obtaining improved epitope density on (+)-methamphetamine conjugate vaccines. J Med Chem. 2011;54(14):5221–5228.
20. Moreno AY, Mayorov AV, Janda KD. Impact of distinct chemical structures for the development of a methamphetamine vaccine. J Am Chem Soc. 2011;133(17):6587–6595.

• **This paper provides a good introduction on the importance of distinct structure of METH and its analogues for the developemnt of METH vaccine and METH specific antibody in animal model**

21. Miller ML, Moreno AY, Aarde SM, et al. A methamphetamine vaccine attenuates methamphetamine-induced disruptions in thermoregulation and activity in rats. Biol Psychiatry. 2013;73(8):721–728.
22. Collins K, Schlosburg J, Lockner J, et al. Lipid tucaresol as an adjuvant for methamphetamine vaccine development. Chem Commun 2014;50(31):4079–4081.
23. Chen Y-H, Wu K-L, Tsai H-M, et al. Treatment of methamphetamine abuse: an antibody-based immunotherapy approach. J Food Drug Anal. 2013;21(4):S82–S86.
24. Chen Y-H, Chen C-H. The development of antibody-based immunotherapy for methamphetamine abuse: immunization, and virus-mediated gene transfer approaches. Curr Gene Ther. 2013;13(1):39–50.
25. Bonese K, Wainer B, Fitch F, et al. Changes in heroin self-administration by a rhesus monkey after morphine immunisation. Nature. 1974;252(5485):708–710.
26. Kosten T, Owens SM. Immunotherapy for the treatment of drug abuse. Pharmacol Ther. 2005;108(1):76–85.
27. Peterson EC, Gunnell M, Che Y, et al. Using hapten design to discover therapeutic monoclonal antibodies for treating methamphetamine abuse. J Pharmacol Exp Ther. 2007;322(1):30–39.
28. Byrnes-Blake KA, Laurenzana EM, Landes RD, et al. Monoclonal IgG affinity and treatment time alters antagonism of (+)-methamphetamine effects in rats. Eur J Pharmacol. 2005;521(1–3):86–94.
29. Shen XY, Kosten TA, Lopez AY, et al. A vaccine against methamphetamine attenuates its behavioral effects in mice. Drug Alcohol Depend. 2013;129(1–2):41–48.
30. Moreno AY, Azar MR, Warren NA, et al. A critical evaluation of a nicotine vaccine within a self-administration behavioral model. Mol Pharm. 2010;7(2):431–441.
31. Cheng L, Kim S, Chung A, et al. Amphetamines: new radioimmunoassay. FEBS Lett. 1973;36(3):339–342.
32. Choi MJ, Gorovits BM. A visual membrane immunoassay for the detection of methamphetamine using an enzyme-labeled tracer derived from methamphetamine and amphetamine. Biol Pharm Bull. 1994;17(7):875–880.
33. Choi J, Choi MJ, Kim C, et al. The optimization of ELISA for methamphetamine determination: the effect of immunogen, tracer and antibody purification method on the sensitivity. Arch Pharm Res. 1997;20(1):46–52.
34. Choi J, Kim C, Choi MJ. Immunological analysis of methamphetamine antibody and its use for the detection of methamphetamine by capillary electrophoresis with laser-induced fluorescence. J Chromatogr B. 1998;705(2):277–282.
35. Olson ME, Sugane T, Zhou B, et al. Consequence of hapten stereochemistry: an efficacious methamphetamine vaccine. J Am Chem Soc. 2019;141(36):14089–14092.

• **This review article provides a good update on the vaccine developemnt for the drug of abuse including METH**

36. Kinsey B. Vaccines against drugs of abuse: where are we now? Ther Adv Vaccines. 2014;2(4):106–117.

• **This article provides interesting insight on the METH vaccine efficacy based on gender of the animal**

37. Nguyen J, Bremer P, Hwang C, et al. Effective active vaccination against methamphetamine in female rats. Drug Alcohol Depend. 2017;175:179–186.
38. Rüedi-Bettschen D, Wood SL, Gunnell MG, et al. Vaccination protects rats from methamphetamine-induced impairment of behavioral responding for food. Vaccine. 2013;31(41):4596–4602.
39. Haile CN, Kosten TA, Shen XY, et al. Altered methamphetamine place conditioning in mice vaccinated with a succinyl-methamphetamine-tetanus-toxoid vaccine. Am J Addict. 2015;24(8):748–755.
40. Arora R, Haile CN, Kosten TA, et al. Preclinical efficacy of an anti-methamphetamine vaccine using E6020 adjuvant. Am J Addict. 2019;28(2):119–126.
41. Michael Owens S, Atchley T. Monoclonal antibodies as pharmacokinetic antagonists for the treatment of (+)-methamphetamine addiction. CNS & Neurol Disord Drug Targets. 2011;10(8):892–898.
42. Gentry WB, Rüedi-Bettschen D, Owens SM. Anti-(+)-methamphetamine monoclonal antibody antagonists designed to prevent the progression of human diseases of addiction. Clin Pharmacol Ther. 2010;88(3):390–393.
43. Lu R-M, Hwang Y-C, Liu I-J, et al. Development of therapeutic antibodies for the treatment of diseases. J Biomed Sci. 2020;27(1):1–30.
44. Delves PJ, Roitt IM. Encyclopedia of immunology. Academic Press; 1998.
45. Waldmann H. Human monoclonal antibodies: the benefits of humanization. Springer; 2019. p. 1–10.
46. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004;93(11):2645–2668.
47. Laurenzana EM, Byrnes-Blake KA, Milesi-Hallé A, et al. Use of anti-(+)-methamphetamine monoclonal antibody to significantly alter (+)-methamphetamine and (+)-amphetamine disposition in rats. Drug Metab Dispos. 2003;31(11):1320–1326.
48. McMillan D, Hardwick W, Li M, et al. Effects of murine-derived anti-methamphetamine monoclonal antibodies on (+)-methamphetamine self-administration in the rat. J Pharmacol Exp Ther. 2004;309(3):1248–1255.
49. Daniels J, Wessinger W, Hardwick W, et al. Effects of anti-phencyclidine and anti-(+)-methamphetamine monoclonal antibodies alone and in combination on the discrimination of phencyclidine and (+)-methamphetamine by pigeons. Psychopharmacology (Berl). 2006;185(1):36–44.
50. Stevens MW, Henry RL, Owens SM, et al. First human study of a chimeric anti-methamphetamine monoclonal antibody in healthy volunteers. Taylor & Francis; 2014. p. 1649–1656.
51. Apostolopoulos V, Lofthouse SA, Popovski V, et al. Peptide mimics of a tumor antigen induce functional cytotoxic T cells. Nat Biotechnol. 1998;16(3):276–280.
52. Apostolopoulos V, Osinski C, McKenzie IF. MUC1 cross-reactive Gal alpha(1,3)Gal antibodies in humans switch immune responses from cellular to humoral. Nat Med. 1998;4(3):315–320.
53. Karanikas V, Hwang LA, Pearson J, et al. Antibody and T cell responses of patients with adenocarcinoma immunized with mannan-MUC1 fusion protein. J Clin Invest. 1997;100(11):2783–2792.