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Treatment of rats with an anti-(+)-methamphetamine monoclonal antibody shortens the duration of action of repeated (+)-methamphetamine challenges over a one month period

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ABSTRACT

This study assessed clinical scenarios of continuing monoclonal antibody (mAb) treatment for (+)-methamphetamine (METH) addiction, and the implications of missing or discontinuing this therapy. We hypothesized that chronic anti-METH mAb7F9 (METH K_D = 9 nM) treatment of rats could significantly decrease METH-induced behaviors; even with repeated METH challenges, use of METH doses in excess of mAb binding sites, and after discontinuing mAb treatment which results in a 10-fold reduction in mAb7F9 serum concentrations. Male Sprague Dawley rats (n = 6/group) were treated with i.v. saline or a loading dose of mAb7F9 to achieve instant steady-state conditions followed by two weekly (141 mg/kg) doses ending on day 14. METH (0.56 mg/kg) was administered 4 h and three days after each saline or mAb7F9 treatment, and on day 21. This produced locomotion and rearing behavior that lasted about 120 min in control rats. In mAb7F9 treated rats, METH-induced distance traveled was significantly reduced from 60 to 120 min (P < 0.05) on days 0–21 and rearing was significantly reduced from 60 to 120 min on days 0–17. METH serum concentrations determined 5 h after METH dosing was significantly increased in mAb7F9-treated rats after all METH challenges. On days 24 and 28 (the final day), the rats were administered a 3-fold higher METH dose (1.68 mg/kg). MAb7F9 treated rats showed a substantially earlier termination of the METH-induced locomotion on both days, even though the METH dose exceeded mAb7F9s binding capacity. METH brain concentrations determined 5 h after METH on day 28 were also significantly decreased in mAb7F9-treated rats. In conclusion, over one month, mAb7F9 significantly and continuously bound METH and reduced METH-induced locomotor effects even after discontinuation of mAb treatment and challenge with higher METH doses.

1. Introduction

METH addiction produces a chronic relapsing cycle of habitual, compulsive drug use which includes binge use, intoxication, withdrawal, and craving [1]. The positive reinforcement of METH is the most common cause for both continued use and relapse [2]. Unfortunately, small molecule treatments for relapse prevention have been unsuccessful [3].

High affinity, anti-METH monoclonal antibodies (mAb) could potentially decrease the rewarding effects of METH, and thereby lessen the impact of a relapse to METH use [4]. The anti-METH mAb rapidly binds METH in the bloodstream. This decreases both the rate of entry and the amount of METH in the brain [5]. Clearance of METH (e.g., metabolism) is also a significant mechanism for regenerating mAb binding capacity for METH [6].

Abbreviations: AMP, (+)-amphetamine; i.v., intravenous; AMP-d_{11}, 1,1,2,3,3,3-hexadeutero-1-pentadeuterophenyl-2-aminopropane; K_D, equilibrium dissociation rate constant; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; mAb, monoclonal antibody; METH, (+)-methamphetamine; METH-d_5, (±)-1-phenyl-1,2-dideutero-2-[trideuteromethyl]aminopropane; s.c., subcutaneous; $t_{1/2}$, terminal elimination half-life.

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Considering their high specificity for METH-like drugs [7] and non-hepatic metabolism [8], anti-METH mAbs could be safely co-administered with small molecule therapies for existing medical conditions. MAb medication should also lack abuse liability and significant adverse effects [4,6]. The main disadvantages are cost and the potential for eventual anti-mAb immune responses.

Anti-METH mAbs can acutely block METH-induced effects in rats [7,9,10], but there is limited data on anti-METH antibody therapy blocking METH effects over an extended period of time, and at METH doses in significant excess of antibody binding capacity [11,12]. These therapeutic attributes are important because METH-addicted patients are unlikely to remain abstinent from METH use even during treatment and are likely to miss scheduled treatments. For example, in a 16 week clinical study, only 30% of the weekly METH urine screens were negative and only one-third of the patients completed the study [13].

Treatment of METH relapse will require a course of medication lasting for months. To sustain long-term steady-state concentrations within a therapeutic window, a good practice is to administer medications at a rate of once every drug half-life ($t_{1/2}$). Typically, mAb therapies have a 3–4 week $t_{1/2}$ in humans, therefore a patient would only need mAb therapy every 3–4 weeks [8]. This is in stark contrast to small molecule medications with a 12 h $t_{1/2}$ (for example) that would require daily or twice daily administration [14–17]. The need for less frequent mAb doses could have significant benefits for patient convenience and compliance.

The current study was performed to assess clinical scenarios of chronic mAb treatment for METH addiction, and the implications of missing or discontinuing mAb treatments. We hypothesized that chronic anti-METH mAb7F9 treatment of rats could significantly decrease METH-induced behaviors; even with repeated METH challenges, use of METH doses in excess of mAb binding sites, and after stopping or missing mAb treatments. Over the one-month study, MAb7F9 significantly and continuously reduced METH-induced locomotor effects, produced substantial METH serum binding, and still had the capacity to lower brain METH concentrations on day 28.

2. Methods

2.1. Drugs and chemicals

(+)-METH hydrochloride and (+)-amphetamine (AMP) sulfate were obtained from NIDA (Rockville, MD). Analytical internal standards and all other chemicals were purchased from Sigma–Aldrich (St. Louis, MO). Doses and standards were calculated as the free base.

2.2. Anti-METH mAb

Discovery and large-scale production of mAb7F9 (mouse IgG1 isotype, κ light chain, K_D = 9 nM for METH) are previously described [7,18,19]. A chimeric version of mAb7F9 is in the process of human clinical trials [6]. The $t_{1/2}$ of mAb7F9 in rats was estimated to be 7 days based on $t_{1/2}$ values of three other IgG anti-METH mAbs from our laboratory [20].

2.3. Animals

Male Sprague-Dawley rats (n = 16) with dual indwelling jugular vein catheters were obtained from Charles River Laboratories (Wilmington, MA). Rats were housed separately, provided water ad libitum, and fed sufficient food pellets to maintain a 300 g body weight. All experiments were conducted in accordance with the NIH Guide for Care and Use of Laboratory Animals, and the University of Arkansas for Medical Sciences Animal Care and Use Committee.

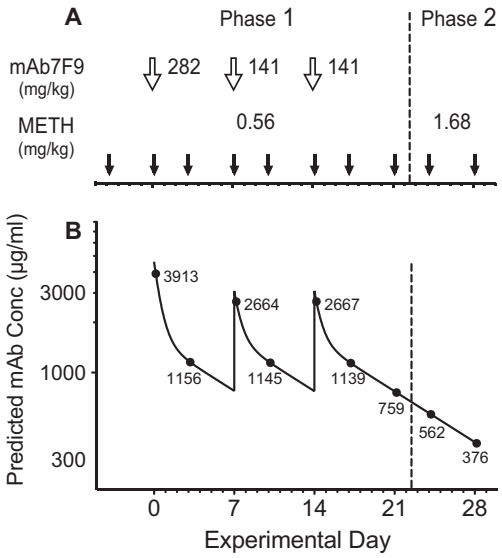

Fig. 1. (A) Experimental protocol for dosing with vehicle or mAb7F9 treatment (open arrows) and METH challenges (closed arrows). Doses of mAb7F9 and METH are shown for each study. The dashed line is included to indicate transition from Phase 1 to Phase 2. (B) Predicted serum mAb7F9 concentrations over time (solid line) and predicted mAb concentrations at the times of each METH challenge (black dots, actual values included). After each METH challenge (closed arrows), locomotion and rearing were measured for 4 h. Blood samples were collected 5 h after all METH doses. Brains and trunk blood were collected after the final METH challenge on day 28.

2.4. Experimental design

Rats were acclimated to home cages and handling for one-week. They were then habituated 6 h a day for 4 days (and 1 day before experiments) in open-top polyethylene behavioral chambers (60 cm × 45 cm × 40 cm). Rats were administered 0.56 mg/kg METH every three days to obtain stable METH-induced locomotion. Data from the third dose was used to match-pair rats into vehicle and mAb7F9 treatment groups (n = 8/group).

Phase 1 of the studies began 4 days after the last METH conditioning dose. The vehicle and mAb7F9 treatments were administered 4 h before i.v. METH challenge doses (see Fig. 1A). For mAb7F9, an i.v. loading dose (over 1.5 min) on day 0 was used to achieve immediate steady-state concentrations, followed by two weekly maintenance doses (on days 7 and 14, over 0.75 min) [21]. The maintenance dose of mAb7F9 was calculated to be 0.5 M in binding sites to the total body burden of a single 0.56 mg/kg METH dose.

2.5. Behavioral studies

On METH challenge days (Fig. 1A), rats were acclimated in the chamber for 1.5 h before METH administration. Movement was recorded by overhead video cameras for 5.5 h. Ethovision 8 software (Noldus Information Technology, Inc., Sterling, VA) measured locomotion as horizontal distance traveled in 4 min bins. We also validated a method to quantitate rearing events, based on Noldus instructions [22]. We defined a rearing event as a reduction in body surface area of ≥20% of the running average of the previous 3 s.

We analyzed locomotion and rearing data from each 4 h experiment in both 1 h intervals and as 4 h of total response. We also calculated duration of activity [7] and time of peak activity.