Effects of Murine-Derived Anti-Methamphetamine Monoclonal Antibodies on (+)-Methamphetamine Self-Administration in the Rat


Department of Pharmacology and Toxicology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas (D.E.M., W.C.H., M.L., M.G.G., S.M.O.); and Chemistry and Life Sciences, Research Triangle Institute, Research Triangle Park, North Carolina (F.I.C., P.A.)

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ABSTRACT

Two murine-derived anti-methamphetamine monoclonal antibodies were studied as potential pharmacokinetic antagonists of (+)-methamphetamine self-administration by rats. Intravenous administration of a 1 g/kg dose of the lower affinity [antibody equilibrium dissociation constant (Kd) = 250 nM] monoclonal antibody (mAb) designated mAb6H8, 1 day before the start of several daily 2-h self-administration sessions produced effects that depended on the dose of (+)-methamphetamine. mAb6H8 increased the rate of self-administration of a unit dose of 0.06 mg/kg (+)-methamphetamine, had little effect on the rate of self-administration of a unit dose of 0.03 mg/kg (+)-methamphetamine, and lowered the rate of self-administration of a unit dose of 0.01 mg/kg (+)-methamphetamine to a level similar to that after saline substitution. mAb-induced changes in rates of self-administration occurred very early in self-administration sessions and lasted for 3 to 7 days. Intravenous administration of a 1 or a 0.6 g/kg dose of a higher affinity (Kd = 11 nM) mAb designated mAb6H4, 24 h before the first of several self-administration sessions, produced very similar effects to the lower affinity mAb, despite the more than 20-fold greater affinity for (+)-methamphetamine. It is proposed that these anti-methamphetamine antibodies bind some of the self-administered (+)-methamphetamine before it can penetrate into brain, thereby reducing the amount of free drug available to function as a reinforcer. Although neither of these mAb medications are optimal antibodies for treating (+)-methamphetamine abuse, the experiments demonstrate that anti-(+)-methamphetamine monoclonal antibodies can attenuate the self-administration of the drug and suggest the potential of using monoclonal antibodies as pharmacokinetic antagonists of (+)-methamphetamine.

The abuse of amphetamines is a serious worldwide problem. Since 1999, there has been a steady upward trend in the number of drug-related emergency department visits in the United States (DAWN, 2003). The United Nations Office on Drugs and Crime estimates that approximately 0.6% of the global population has used amphetamines and the rate of use is increasing, especially in China and East Europe (http://www.unodc.org). The National Drug Threat Assessment states that methamphetamine is “a principal drug threat” to the United States and that 31% of state and local law enforcement agencies nationwide consider it as the principal drug threat (National Drug Intelligence Center, 2003).

Despite the serious consequences of abuse of the amphetamines, there is no accepted pharmacotherapy for treatment of the amphetamine user. Recently, there has been increasing interest in the use of antibodies as possible pharmacotherapeutic agents for the treatment of drug abuse. Either passive or active immunization with antibodies has been reported to attenuate the pharmacological effects or lower brain levels of heroin (Killian et al., 1978), phencyclidine (Valentine and Owens, 1996; Hardin et al., 2002), nicotine (Hieda et al., 1999; Pentel et al., 2000; Tuncok et al., 2001), cocaine (Baird et al., 2000; Kantak et al., 2000; Carrera et al., 2001; Koetzner et al., 2001), and methamphetamine (Byrnes-Blake et al., 2001; McMillan et al., 2002). The drug effects that have been decreased by anti-drug antibodies include locomotor activity (Pentel et al., 2000; Byrnes-Blake et al., 2001; Carrera et al., 2001; Hardin et al., 2002), seizures (Tuncok et al., 2001), increases in blood pressure (Pentel et al., 2000; Brisco et al., 2001), drug self-administration (Mets et al., 1998; Baird et al., 2000; Carrera et al., 2000; Kantak et al., 2000), stereotypy (Carrera et al., 2001), fixed-ratio re-

ABBREVIATIONS: mAb, monoclonal antibody; Kd, antibody equilibrium dissociation constant; FR 3, fixed ratio 3.
sponding for food (Koetzner et al., 2001), and drug discrimination (McMillan et al., 2002). It is usually assumed that the primary mechanism by which the anti-drug antibody produces its effects is through high-affinity binding to the drug, thereby preventing access of the drug to its sites of action including the brain (Valentine and Owens, 1996; Hieda et al., 1999; Pentel et al., 2000; Proksch et al., 2000; Hardin et al., 2002).

Recently, we have shown that an anti-(-)-methamphetamine mouse monoclonal antibody (mAb; will be used as both a singular and plural abbreviation) with a $K_d$ for (+)-methamphetamine of 250 nM (designated mAb6H8) produced a 3-fold shift to the right in the dose-response curve for the discrimination of (+)-methamphetamine in both rats and pigeons (McMillan et al., 2002). Although the discriminative stimulus properties of drugs probably contribute to their reinforcing properties, the animal model that is used most frequently to access the reinforcing properties of a drug in animals is the intravenous self-administration model. In the present experiment, we studied the potential of a relatively low- and a relatively high-affinity mouse monoclonal anti- (+)-methamphetamine mAb for blocking the intravenous self-administration of (+)-methamphetamine.

Materials and Methods

Subjects. Subjects for the data reported in the present experiments were male Sprague-Dawley rats. At the beginning of training, rats were approximately 3 months old and averaged 300 g in weight. They were maintained at these weights during the course of the experiment by controlled feeding. They were housed in a vivarium with a 12/12-h light/dark session with illumination beginning at 7:00 AM each day. There was free access to water in the home cage but not in the test chamber.

Apparatus. The test chamber was a Gerbrands (Arlington, MA) model G7410 operant chamber measuring 23 cm long, 22 cm wide, and 19 cm high. The test chamber contained a Gerbrands model G6311 response lever mounted on the right side of the chamber 2 cm from the side wall and 9 cm above the floor. A downward force of approximately 15 g was required to operate the lever. Two 24-V DC lights were mounted in the ceiling at the rear of the test chamber. These lights were turned on during the entire 2-h session. The lights were frequently to access the reinforcing properties of a drug in animals is the intravenous self-administration model. In the present experiment, we studied the potential of a relatively low- and a relatively high-affinity mouse monoclonal anti- (+)-methamphetamine mAb for blocking the intravenous self-administration of (+)-methamphetamine.
graph made the use of analysis of variance problematic, so Student’s t test or paired Student’s t tests were used for statistical analysis. This approach was dictated by the limited supply of (+)-methamphetamine mAbs and the difficulties in maintaining the venous cannulae for extended periods of time. When statistical tests were conducted, data were used from several days. For example, in Figs. 3 and 4, the baseline responding for the 4 days prior to mAb administration were compared with the responding during the 3 or 4 days after administration of the mAb using Student’s t tests with the level of statistical significance set at 0.05.

Results

The first experiment was performed with two groups of rats trained to self-administer 0.06 mg/kg unit doses of (+)-methamphetamine, a unit dose chosen on the basis of data from Munzar et al. (1999). Figure 1 shows data from these rats for the final four sessions of training before administration of mAb6H8. Both groups of rats averaged about 30 injections during the 2-h test period, resulting in a self-administered dose of about 1.8 mg/kg. Subsequently, saline was substituted for (+)-methamphetamine in one group of rats (unfilled circles). When saline replaced the 0.06 mg/kg unit dose of (+)-methamphetamine, there was an immediate and marked reduction in the rate of responding by these rats. The second group of rats (filled circles) received a 1 g/kg dose of mAb6H8 20 h before the next session, during which (+)-methamphetamine injections continued to be available at the same 0.06 mg/kg dose. Rather than producing a reduction in the number of injections earned as occurred when saline was substituted for (+)-methamphetamine, in the presence of mAb6H8, the rate of responding almost doubled, and the effect continued for 7 days. Subsequently, saline was substituted for (+)-methamphetamine in the rats that had received mAb6H8. The responding of these rats decreased immediately, as had occurred when saline was substituted for (+)-methamphetamine in the group that had not received the mAb. When access to (+)-methamphetamine was restored for the group that had undergone saline substitution (days 8–13) but had not received mAb6H8, the rats responded by self-administering the baseline number of (+)-methamphetamine injections. The changes in the number of injections produced by both saline substitution and administration of mAb6H8 were significantly different from the baseline rate of injections (P < 0.05).

We reasoned that the apparent failure of 1 g/kg mAb6H8 to block the effects of 0.06 mg/kg doses of (+)-methylamphetamine might depend on the unit dose of the drug. Therefore, we studied the effects of mAb6H8 on the self-administration of additional unit doses of (+)-methamphetamine (Fig. 2). All rats shown in Fig. 2 first were trained to self-administer 0.06 mg/kg unit doses of (+)-methamphetamine under the FR 3 schedule before other unit doses of (+)-methamphetamine were studied. The top frame of Fig. 2 shows unit dose response data for (+)-methamphetamine self-administration by rats at each unit dose. After responding had stabilized at each unit dose, rats self-administered the highest number of injections during the 2-h session at the 0.01 mg/kg unit dose.
of (+)-methamphetamine, with very few injections self-administered at the next lower dose (0.003 mg/kg/injection). Unit doses greater than 0.01 mg/kg produced a progressive decrease in the number of (+)-methamphetamine self-administrations. The relationship between unit dose and response rate for the self-administration of amphetamines has been described as an inverted U (Yokel and Pickens, 1973), and this relationship can be seen from the dose-response curves shown in Fig. 2. Since the 0.06 mg/kg unit dose fell on the descending leg of this inverted U-shaped curve, a partial pharmacokinetic antagonism of the 0.06 mg/kg unit dose of (+)-methamphetamine might have caused this dose to produce effects similar to lower unit doses (moving its effect upward and to the left on the descending leg of the dose-response curve), resulting in increased responding.

The bottom frame of Fig. 2 shows the same data plotted as total milligrams per kilogram of (+)-methamphetamine self-administered. Very little self-administration of (+)-methamphetamine occurred at the 0.003 mg/kg unit dose. Higher unit doses of (+)-methamphetamine resulted in higher doses self-administered; however, there was little difference in the total dose self-administered during the 2-h sessions across a range of 0.03 to 0.3 mg/kg unit doses with approximately 2 mg/kg being self-administered across all of these doses.

Data showing the effects of 1 g/kg mAb6H8 on the self-administration of unit doses of (+)-methamphetamine ranging from 0.01 to 0.06 mg/kg are shown in Fig. 3. Different rats had different rates of self-administration; therefore, the data were plotted as a percentage of the baseline rate of self-administration for the last four sessions prior to administration of the mAb. The mean dose self-administered by all rats across the 4 days of testing is shown in the lower left-hand corner of each frame. As discussed previously, the mAb6H8 significantly increased the rate of self-administration of the 0.06 mg/kg unit dose of (+)-methamphetamine (frame A), but it failed to produce a statistically significant change in the rate of self-administration of the 0.03 mg/kg unit dose (frame B). However, the mAb almost completely blocked the self-administration of the 0.01 mg/kg unit dose (frame C) to the extent that rates of responding fell to those during saline extinction (frame D). Both the increased rate of self-administration (frame A) and the decreased rate of self-administration (frame C) after administration of mAb6H8 were significantly different from the baseline rate of self-administration (P < 0.001).

Figure 4 shows similar data for the higher affinity mAb6H4 mAb. Column 1 shows the effects of 1 g/kg mAb6H4 on (+)-methamphetamine self-administration. One day following administration of 1 g/kg mAb6H4, the rate of self-administration of the 0.06 mg/kg unit dose of (+)-methamphetamine was significantly increased (P < 0.001, frame A). The baseline rate of responding became erratic during the 4 days when the unit dose of (+)-methamphetamine was decreased to 0.03 mg/kg in the presence of 1 g/kg mAb6H4 (frame B). The 1 g/kg dose of mAb6H4 significantly decreased the rate of responding (P < 0.05) maintained by the 0.01 mg/kg unit dose of (+)-methamphetamine by about 50% (frame C). A dose of 0.6 g/kg of mAb6H4 also blocked the self-administration of 0.03 mg/kg doses of (+)-methamphetamine (P < 0.001, frame D), but a 0.3 g/kg dose of the mAb failed to block the effects of unit doses of 0.06 or 0.03 mg/kg unit doses (frames E and F).

Figure 5 shows an analysis of the pattern of (+)-methamphetamine self-administration within 12-min segments of the daily 2-hour self-administration sessions.
2-h session for 0.06 mg/kg unit doses of (+)-methamphetamine. The highest percentage of (+)-methamphetamine self-administrations of 0.06 mg/kg unit doses occurred during the first 12 min of the session. When saline was substituted for (+)-methamphetamine (bottom frame), responding decreased markedly during the first 12 min of the session and remained at a very low rate throughout the remainder of the session. When the rat self-administered the 0.06 mg/kg unit dose of (+)-methamphetamine in the presence of 1.0 g/kg of mAb6H8, rates of responding increased during each of the first three 12-min segments of the session. Then, the rate of responding remained close to the rate that occurred for the 0.06 mg/kg unit dose without the mAb for the remainder of the session.

Figure 6 shows the pattern of self-administration of the 0.01 mg/kg unit dose during the last three sessions before administration of 1 g/kg mAb6H8 and during the first three sessions after administration of the mAb. At this low unit dose of (+)-methamphetamine, responding gradually increased over the session. Rates of responding were quite variable across subjects. Nevertheless, the effects of the mAb occurred rapidly. The rate of responding was only slightly decreased during the first 12 min of the session after the mAb, but subsequently, the rates of responding in the presence of the mAb remained at very low levels relative to the rates of responding prior to administration of mAb6H8.

**Discussion**

The anti-(+)-methamphetamine mAb6H8 and mAb6H4 increased the rate of self-administration of a 0.06 mg/kg unit dose of (+)-methamphetamine, appeared to have minimal effects on a 0.03 mg/kg unit dose, and markedly decreased the self-administration of a 0.01 mg/kg unit dose. mAb6H8 reduced the rate of (+)-methamphetamine self-administration at the 0.01 mg/kg unit dose to about the same level as when saline solution was substituted for a 0.06 mg/kg unit dose of (+)-methamphetamine. The effects of anti-methamphetamine mAb on the self-administration of (+)-methamphetamine lasted from 4 to 7 days. Since the unit dose-response curve for (+)-methamphetamine self-administration has the shape of an inverted U, these data are consistent with the interpretation that the mAb produced a partial pharmaco-
methamphetamine. Under these conditions, the rats respond at higher rates and partially surmount the pharmacokinetic antagonism. At the lowest unit doses, it is suggested that the mAbs bind a higher percentage of (+)-methamphetamine molecules so that very little drug reaches the brain. This greatly decreases the reinforcing efficacy of these lower unit doses to produce effects similar to those produced by saline substitution. These data are consistent with our previous observations (McMillan et al., 2002) that mAb6H8 can attenuate the discriminative stimulus effects of (+)-methamphetamine for 4 to 7 days.

Other investigators have shown that anti-drug antibodies can alter the disposition of drugs between blood and brain. For example, it has been shown that the administration of a monoclonal anti-phencyclidine Fab fragment with a high affinity for phencyclidine (K_d = 1.8 nM) can rapidly and dramatically decrease brain phencyclidine concentrations, whereas increasing phencyclidine levels in serum (Valentine and Owens, 1996). These experiments showed that most of the phencyclidine in serum was bound to the mAb. In the present experiments, the mAb was given a day before the rats had an opportunity to self-administer (+)-methamphetamine. When animals had been pretreated with the mAb a day before the next opportunity to self-administer (+)-methamphetamine, the mAb should have been available to bind at least part of the self-administered dose of (+)-methamphetamine before it reaches the brain. At low unit doses of (+)-methamphetamine, the mAb may bind enough (+)-methamphetamine to prevent its entry into the brain and block its reinforcing effect.

It may be more difficult for anti-drug antibodies to block the self-administration of some drugs than to reverse the effects of overdose. In the case of drug overdose, the drug usually is already well distributed in the blood and tissues including the brain. Administration of the mAbs intraventricularly is a more effective way than pretreatment to block the effects of overdose. The latter may not be practical for treatment, but it is possible that the mAbs can be used for treatment if given immediately after an overdose.
nously should begin to bind the drug in serum, thereby disrupting the equilibrium of unbound drug between brain and blood. Favorably shifting this equilibrium by binding of (+)-methamphetamine in serum should cause unbound drug to move from the brain to the serum, where it becomes accessible to additional binding by the mAb. For the prevention of drug self-administration, the problem is potentially more difficult, especially under the conditions where the drug is administered very rapidly (1.3 s) in a small volume (0.7 ml), as occurred in our experiments. In these experiments, when (+)-methamphetamine self-administration was initiated 1 day after administration of the anti-methamphetamine mAb, the mAb should have been well distributed in serum. The intravenous self-administration of each (+)-methamphetamine unit dose is delivered rapidly in a small bolus that enters the venous return to the heart, where it is flushed rapidly into areas with high blood flow such as the brain. The small volume of blood and limited amount of mAb in that volume of blood in which the drug is transported, plus the limited amount of time that the mAb has to bind to the drug before the free drug enters tissues like the brain, may not be enough to prevent some (+)-methamphetamine molecules that are not bound to the mAb from reaching the brain to produce reinforcing effects. It is suggested that this is why the mAbs were not able to block the self-administration of higher unit doses of (+)-methamphetamine. Some of the drug still must have been getting to the brain to produce a reinforcing effect sufficient to maintain responding. As more (+)-methamphetamine is self-administered, more and more of the binding sites on the mAb would be occupied with (+)-methamphetamine molecules, so that subsequent self-administrations produce more free (+)-methamphetamine which can cross the blood-brain barrier thereby partially or completely surmounting the pharmacokinetic antagonism.

Nevertheless, other investigators have been able to block the self-administration of some abused drugs with much lower doses of mAb. For example, Fox et al. (1996) were able to block the self-administration of 1 mg/kg unit doses of cocaine using a 4 mg dose of a monoclonal antibody, but Kantak et al. (2000) required 12 mg of antibody to block this dose of cocaine self-administration. The difference between these studies was that in the Kantak et al. (2000) study, the rate of cocaine infusion was faster (3–4 s) than that (6–8 s) in the study by Fox et al. (1996). In the experiments by Fox et al. (1996), cocaine was available under a second order schedule where a dose of cocaine was available only once every 5 min further limited the rate at which cocaine could be self-administered relative to the rate of (+)-methamphetamine self-administration in the present experiments. In the present experiments, (+)-methamphetamine was available under a FR 3-response schedule whereby doses could be repeatedly administered within a few seconds of each other and the infusion rate was more rapid (1.3 sec) than in either the Fox et al. (1996) or the Kantak et al. (2000) studies. It is possible that the slower rate of delivery and the more limited access to cocaine can be more easily blocked by an antibody than under the current conditions where there is a relatively rapid rate of access to (+)-methamphetamine and a very short duration of drug delivery.

Under our FR 3 schedule, each delivery of (+)-methamphetamine requires only three lever presses by the animal, which require only a few seconds to complete. Following a self-administration, reductions in the concentrations of free (unbound) (+)-methamphetamine due to its binding to mAb might be overcome by rapid self-administrations of additional (+)-methamphetamine under this short FR schedule. Figure 5 shows that at the beginning of the session the rate of self-administration of 0.06 mg/kg unit doses of (+)-methamphetamine was higher after mAb administration than it was without the mAb but that partway through the session, the rate of responding for (+)-methamphetamine leveled off and became similar to the rate of responding in the absence of the mAb. These data suggest that rats self-administer (+)-methamphetamine rapidly at the beginning of the session to reach a steady state, after which the steady-state concentration is maintained by a slower rate of responding for the remainder of the session. In clinical practice, this is commonly referred to as a loading dose, which allows a more rapid achievement of therapeutic levels of the drug. Perhaps the higher rate of (+)-methamphetamine self-administration early in the session is comparable with a loading dose, whereby rats rapidly self-administer (+)-methamphetamine to produce an optimal brain level of the drug. In the presence of mAb, an even higher rate of self-administration of (+)-methamphetamine early in the session would eventually result in occupancy of most of the mAb receptor sites while allowing some free (+)-methamphetamine to reach the brain. Subsequently, the slower rate of responding would maintain the usual steady-state concentration of free drug.

Since there is a significant amount of conversion of (+)-methamphetamine to (+)-amphetamine in the male rat, and these anti-methamphetamine mAbs do not bind to (+)-amphetamine to a significant extent (Byrnes-Blake et al., 2001, 2003), it is possible that (+)-amphetamine might have limited the degree to which mAb could block the self-administration of (+)-methamphetamine. However, (+)-amphetamine is not likely to be a limiting factor in the pharmacokinetic antagonism of (+)-methamphetamine in these experiments for several reasons. First, (+)-methamphetamine enters the brain within a few minutes after intravenous administration (Laurenzana et al., 2003), and it is likely that the reinforcing effect of the drug occurs well before significant conversion of (+)-methamphetamine to (+)-amphetamine occurs. Furthermore, (+)-methamphetamine bound to mAb is protected from metabolism. For these reasons, it is not likely that the conversion of (+)-methamphetamine to (+)-amphetamine is limiting the ability of the mAb to block (+)-methamphetamine self-administration, especially within the first few minutes of the session.

The effects of mAb6H8 on (+)-methamphetamine self-administration occurred rapidly. Both increases (Fig. 5) and decreases (Fig. 6) in self-administration occur early in the session. The time course of the block of 0.01 mg/kg doses of (+)-methamphetamine by mAb6H8 was very similar to the time course of effects when saline was substituted for the drug, suggesting that mAb6H8 was producing an extinction-like effect of the self-administration of the 0.01 mg/kg unit dose.

A puzzling observation in the present experiments is the lack of difference in the effectiveness of mAb6H8 and mAb6H4 as pharmacokinetic antagonists of (+)-methamphetamine. The initial experiments were performed with mAb6H8, which has a $K_d$ of 250 nM for (+)-methamphetamine. When only a partial antagonism of (+)-methamphetamine self-administration is observed, it is often due to the presence of a second receptor type or a second mechanism of action for the drug. In this case, (+)-amphetamine, a metabolite of (+)-methamphetamine, may be responsible for the remaining reinforcing effects. (+)-Amphetamine is known to be a more potent reinforcer than (+)-methamphetamine (Byrnes-Blake et al., 2001), and it is possible that (+)-amphetamine is responsible for the remaining reinforcing effects. However, (+)-amphetamine is not likely to be a limiting factor in the pharmacokinetic antagonism of (+)-methamphetamine in these experiments for several reasons. First, (+)-amphetamine enters the brain within a few minutes after intravenous administration (Laurenzana et al., 2003), and it is likely that the reinforcing effect of the drug occurs well before significant conversion of (+)-methamphetamine to (+)-amphetamine occurs. Furthermore, (+)-methamphetamine bound to mAb is protected from metabolism. For these reasons, it is not likely that the conversion of (+)-methamphetamine to (+)-amphetamine is limiting the ability of the mAb to block (+)-methamphetamine self-administration, especially within the first few minutes of the session.

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amine was achieved with mAb6H8, it was anticipated that a more complete antagonism would be obtained using an mAb with a significantly higher affinity for (+)-methamphetamine. mAb6H4 has a more than a 20-fold greater affinity (11 nM) for (+)-methamphetamine than mAb6H8, yet there appeared to be little difference in the effectiveness of the two mAbs at the doses we tested. Factors other than the affinity of the drug for the mAb must contribute to the ability of anti-methamphetamine mAb to block (+)-methamphetamine self-administration.

To our knowledge, no other laboratory has demonstrated effectiveness of an anti-methamphetamine mAb in blocking (+)-methamphetamine self-administration. Although the current mAb decreased the self-administration of only the lowest unit dose of (+)-methamphetamine, the data clearly demonstrate the potential feasibility of using passive administration of an mAb to block the self-administration of a drug for which no pharmacotherapy is currently available.

References


Address correspondence to: D.E. McMillan, Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Little Rock, AR 72204. E-mail: DEMcMillan@uams.edu