Pharmacology, Biochemistry and Behavior 98 (2011) 449–454

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Role of dopamine D1- and D2-like receptor mechanisms in drug-seeking following methamphetamine self-administration in rats

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ARTICLE INFO

Article history:
Received 7 December 2010
Received in revised form 28 January 2011
Accepted 7 February 2011
Available online 17 February 2011

Keywords:
Methamphetamine
Self-administration
Reinstatement
Dopamine
D1 receptor
D2 receptor

ABSTRACT

It has been suggested that dopaminergic mechanisms mediate relapse to drug-seeking behavior and both D1- and D2-like receptor mechanisms have been implicated. In contrast to self-administration of other drugs, there is a relative paucity of studies that has examined the pharmacological basis of methamphetamine (MA) seeking. Accordingly, the present study used an animal model of drug-seeking to determine the role of D1- and D2-like receptor mechanisms in relapse to MA abuse. Rats were trained to self-administer MA, and then responding was extinguished by replacing the MA solution with vehicle. Experimenter-administered injections of MA or the dopamine uptake inhibitor, GBR 12909, reinstated extinguished responding in a dose-dependent manner. The D1-like antagonist, SCH 23390 attenuated drug-seeking but the D2-like antagonist, eticlopride, was ineffective. The results suggest that MA-seeking is predominantly mediated by DA D1-like receptor mechanisms. These findings are in contrast to the literature on drug-seeking following self-administration of other drugs, and suggest that relapse to different drugs of abuse may rely upon different DA receptor mechanisms.

1. Introduction

Methamphetamine (MA) has become the second most widely used illicit drug world-wide (Cruickshank and Dyer, 2009), accounting for 68% of amphetamine-type psychostimulant manufacture (UNODC, 2008). Many MA users reported difficulty controlling their drug use despite a strong desire to do so (Cadet et al., 2003; Julien, 2001) and there is a particularly high risk of relapse (Copeland and Sorensen, 2001). The high risk and rate of relapse is a critical obstacle to overcome in treatment (Shaham et al., 2003). Persistent drug craving can lead to relapse even after long periods of abstinence (Epstein et al., 2006; Hartz et al., 2001; Markou, 2009), underscoring the importance of research that identifies the relevant neurobiological mechanisms and neuroadaptations that accompany prolonged drug-taking.

A wealth of data indicates that the reinforcing properties of drugs of abuse, including MA, are mediated by increased dopamine (DA) neurotransmission (Adinoff, 2004; Di Chiara et al., 2004; Marsden, 2006; Wise and Rompre, 1989). Pre-treatment with DA agonists (Munzar et al., 1999; Reichel et al., 2008), and novel antagonists (Dwoskin and Crooks, 2002; Harrod et al., 2001; Neugebauer et al., 2007) decreased MA self-administration and a partial D2 agonist reduced breakpoints under a progressive ratio (PR) schedule of reinforcement (Wee et al., 2007). When self-administration of MA was maintained by a fixed ratio (FR) 1 schedule of reinforcement the dose–response function was shifted downward and to the right following administration of the dopamine D1-like antagonist, SCH 23390, but not the D2-like antagonist, eticlopride (Brennan et al., 2009). Thus, whereas pharmacological manipulations of both D1- and D2-like receptors altered self-administration of other drugs of abuse (Hubner and Moreton, 1991; Le Merrer et al., 2007; Zhang et al., 2010), MA self-administration was altered only by pharmacological manipulations of D1-like mechanisms and was resistant to the effects of D2-like antagonism (Brennan et al., 2009).

Self-administration procedures have also been used effectively to identify the mechanisms underlying reinstatement of drug-seeking behavior and relapse following abstinence. In particular, one model of relapse determines factors that can reinstate responding following extinction of self-administration (de Wit and Stewart, 1981). Using this model, priming injections of self-administered drugs produced drug-seeking behavior in laboratory animals (Sanchis-Segura and Spanagel, 2006; Shaham and Stewart, 1996; Shalev et al., 2002).

Drug-seeking has often been attributed to dopaminergic mechanisms (De Vries et al., 1999; Marinelli et al., 2003; Schmidt and Pierce, 2006; Self, 2004; Stewart, 2000). For example, following extinguished drug self-administration, priming injections of a DA (De Vries et al., 1999; Schmidt and Pierce, 2006), but not a serotonin (5-HT; Burmeister et al., 2003; Schmidt and Pierce, 2006), nor a norepinephrine (NE) transporter inhibitor (Schmidt and Pierce, 2006), reinstated cocaine-

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doi:10.1016/j.pbb.2011.02.010

seeking behavior. Further, support for an important role of DA in the reinstatement of drug-seeking comes from studies demonstrating *cocaine- and heroin-seeking behavior* following priming injections of direct D2-like receptor agonists (De Vries et al., 2002; Self, 2004). In addition, *cocaine- and heroin*-seeking was attenuated by selective D1- and D2-like receptor antagonists (Self, 1998, 2004; Shaham and Stewart, 1996).

Reinstatement of drug-seeking has also been demonstrated following extinguished MA self-administration (Anggadiredja et al., 2004; Hiranita et al., 2010; Moffett and Goeders, 2007; Rogers et al., 2008; Shelton and Beardsley, 2008; Shepard et al., 2004), but the neurobiological mechanisms have yet to be thoroughly investigated. Because MA self-administration was differentially responsive to pharmacological manipulations of D1- and D2-like receptor mechanisms (Brennan et al., 2009) we reasoned that reinstatement of MA-seeking might also be selectively altered by pharmacological manipulations of D1-like receptor mechanisms. A role of DA was investigated in two ways. First, the effects of MA and the selective dopamine uptake inhibitor, GBR 12909, on MA-seeking were measured. Second, the effect of a selective D1- or D2-like antagonist on MA-seeking produced by priming injections of MA was measured.

2. Methods

2.1. Subjects

Male Sprague–Dawley rats (n = 21) were bred in the vivarium at Victoria University of Wellington and were housed in groups of four from weaning until they reached 300–350 g. They were then housed individually in standard polycarbonate cages. The vivarium was temperature (21 °C) and humidity (55%) controlled and was maintained on a 12-hour light/dark cycle (lights on at 0700). All testing began at 1400 h. Food and water were available *ad libitum* except during testing. Principles for laboratory animal care were followed (NIH publication NO. 85–23, rev. 1985), and the laboratory was accredited by the Office of Laboratory Animal Welfare (OLAW). All experimental protocols were approved by the Victoria University Animal Ethics Committee.

2.2. Apparatus

Self-administration training and testing were carried out in operant chambers (Med Associates, ENV 001, Georgia, Vermont, USA), enclosed in sound attenuating boxes. Each chamber contained two levers and a stimulus light. Responses on the right lever ("active lever") resulted in a 0.1 ml drug infusion delivered over 12 s. Coincident with drug delivery was the illumination of the stimulus light located above the active lever. Depressions of the left lever ("inactive lever") were recorded but were without programmed consequence. Drug delivery and data recording were controlled by an interfaced microcomputer utilizing Med Associates software.

2.3. Procedures

2.3.1. Surgery

Chronic indwelling intrajugular catheters were implanted under deep anaesthesia induced by an intraperitoneal (IP) injection of a mixture of ketamine (90 mg/kg) and xylazine (5 mg/kg). Prior to the surgery the anti-inflammatory analgesic, Carprofen® (5 mg/kg, SC, Pfizer Animal Health), was administered. The silastic tubing was inserted into the vein and the distal end was passed subcutaneously to the skull where it was secured using acrylic dental cement adhering to 4 small jeweler's screws. A compound sodium lactate solution (Hartmann's solution, 2 × 6 ml, SC) was then administered to restore electrolyte balance.

Carprofen® (5 mg/kg, SC) was administered on each of the two days following surgery. On each of 5 days following surgery the catheters were flushed with 0.2 ml of a sterile 0.9% saline solution, containing heparin (30 IU/ml) and penicillin G potassium (250,000 IU/ml). At the start of the testing period, and every seven days thereafter, catheter patency was tested with a 0.1 ml infusion of sodium pentobarbital (5.0 mg/kg, IV). Catheter patency was confirmed by immediate loss of the righting reflex. If catheter patency was lost, a second catheter was inserted into the left jugular vein as described above and the rat was given a minimum of three days recovery time during which no testing was conducted.

2.3.2. Daily self-administration

Training and experimental tests were conducted five days per week, Monday to Friday, during two hour daily sessions. At the start of each experimental session, the catheters were flushed with 0.2 ml of the 30 IU/ml heparin/penicillin solution. Immediately prior to beginning an experimental session, rats were transferred from home cages to the experimental room in a plastic carry box. The steel tip of each catheter was attached to microbore tubing connected to a 20 ml syringe in an automatic pump (Razel Model A, 1 rpm motor, Georgia, Vermont, USA). The session began with an experimenter-delivered response on the active lever, which cleared the line of the heparin solution. Following each MA infusion there was 30 s timeout (TO) period during which responding on the active lever was without consequence. At the end of each self-administration session, catheters were flushed with 0.2 ml of a 30 IU/ml heparinized saline solution containing 250,000 IU/ml penicillin G potassium, followed by 0.1 ml of a 30 IU/ml heparinized saline solution containing 8000 IU/ml streptokinase to prevent the formation of fibroids.

2.3.2.1. Acquisition of self-administration. During training, MA (0.1 mg/kg/infusion) was self-administered according to a *fixed ratio (FR) 1* schedule of reinforcement during daily 2 h tests. This dose was based on our preliminary work and that of other studies showing reliable self-administration (Brennan et al., 2009; Shelton and Beardsley, 2008; Stefanski et al., 1999). Self-administration was considered acquired when 1) there were at least 10 infusions earned per session, 2) the ratio of active to inactive lever responses in a session was at least 2:1, and 3) these criteria were met for at least three consecutive days with less than 20% variation in the number of active lever responses. Following at least 10 days of self-administration, and the fulfillment of the above criteria, the schedule of reinforcement was increased to FR2 until there was at least three consecutive days of stable responding, and finally to FR5 for a minimum of 10 days.

2.3.2.2. Drug-seeking. Following stable FR5 responding, operant behavior was extinguished by replacing the drug with a heparinized (3 IU/ml) saline solution, and disconnecting the light stimulus. The vehicle solution was delivered according to an FR5 schedule. Once the number of active lever presses decreased to <20% of baseline tests of drug-seeking were conducted. On the test days, drugs were administered, *and immediately following MA priming injections*, the rats were placed in the self-administration chambers. Responding was reinforced according to an FR5 schedule by the delivery of the vehicle solution and the illumination of the stimulus light that had been paired with self-administered drug infusions during training. Drug-seeking was defined on the basis of increased responding during these tests.

2.3.2.2.1. Experiment 1. Initial tests determined the effects of various doses of experimenter-administered MA (0.0, 1.0 or 2.0 mg/kg, IP, n = 8) on drug-seeking. All rats received all doses of MA administered in a random order. Repeated tests were conducted during a recurring series of self-administration (minimum 2 days), extinction (minimum 2 days), and test days until all rats had been tested with all 3 doses of MA.

2.3.2.2.2. Experiment 2. In the second group, tests of drug seeking produced by the DA uptake inhibitor, GBR 12909 (0.0, 1.0 or 10.0 mg/kg, IP, n = 4) was measured as above. These doses are based on preliminary work and previous studies on the effects of DA agonists on drug-seeking (De Vries et al., 1999; Schenk et al., 2000; Schmidt and Pierce, 2006).

2.3.2.2.3. Experiment 3. On the basis of the MA dose-effect data obtained in experiment 1, subsequent groups were tested with the 2.0 mg/kg dose of MA. Effects of either the D1-like antagonist, SCH 23390 (0.0–0.04 mg/kg, SC, n = 5), or the D2-like antagonist, eticlopride (0.0–0.05 mg/kg, IP, n = 4), on drug-seeking produced by a priming injection of MA (2.0 mg/kg, IP) was measured. Pretreatments were administered in the home cage, 15 (SCH 23390), or 30 (eticlopride) min prior to the MA (2.0 mg/kg, IP) priming-injection. These pretreatment times and doses were based on previous studies from our laboratory (Brennan et al., 2009; Brennan et al., 2007; Daniela et al., 2004). Doses were randomly administered and tests were conducted according to the recurring series outlined above.

2.4. Drugs

Methamphetamine hydrochloride (ESR, Porirua, New Zealand) was dissolved in a sterile 3 IU/ml heparinized 0.9% saline solution for self-administration. GBR 12909 was dissolved in distilled water, while all other drugs (Sigma Aldrich, Australia) were dissolved in a 0.9% saline solution. IV injections were in a volume of 0.1 ml/kg/infusion and systemic injections were in a volume of 1.0 ml/kg. All drug doses refer to the weight of the salt.

2.5. Data analysis

The dose–effect curve for MA-produced drug-seeking, effects of the D1- and D2-like antagonists on MA produced drug-seeking, and drug-seeking produced by GBR12909 were analyzed using separate repeated measures analysis of variance (ANOVA; drug dose × lever). Analyses were conducted using the SPSS statistical package (SPSS Inc., Chicago, Illinois, USA), version 17.0 for Microsoft Windows.

3. Results

3.1. MA self-administration and extinction responding

Fig. 1 shows the average number of responses on the active and inactive levers during two days of responding prior to the start of the reinstatement tests and the last two days of extinction testing.

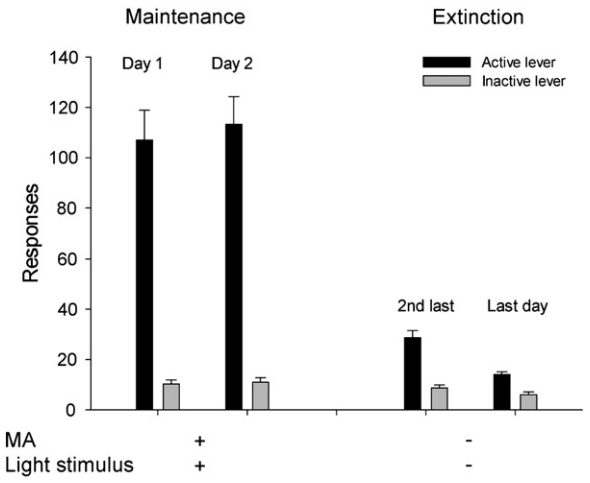

Fig. 1. Mean (+SEM) responding on active, and inactive levers during two days of maintenance and the last two days of extinction (FR5; n = 10).

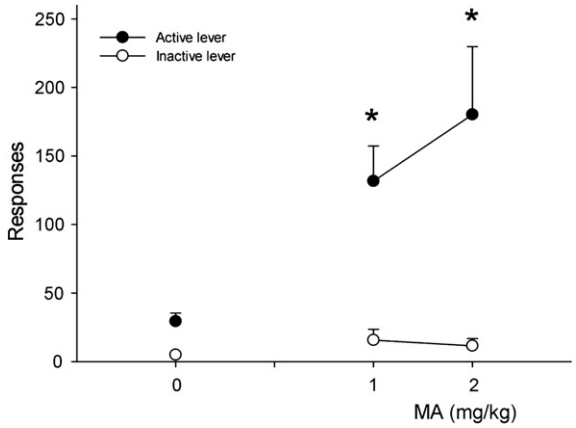

Fig. 2. Mean (+SEM) number of responses during drug-seeking tests as a function of priming injections of MA (0.0, 1.0, 2.0 mg/kg, IP, n = 8). *Significantly different from vehicle ($p<0.05$).

Responding was high during self-administration and when the drug was replaced with vehicle solution and the stimulus light was omitted, active lever responding decreased. Repeated measures ANOVA revealed a significant main effect of condition (self-administration vs. extinction; [$F(1,9) = 38.179$, $p<0.05$]), lever (active vs. inactive; [$F(1,9) = 51.872$, $p<0.05$]), and a significant interaction between these factors [$F(1, 9) = 32.509$, $p<0.05$].

3.2. Experiment 1: MA induced drug-seeking

Fig. 2 shows the effect of MA on drug-seeking behavior. Drug seeking was produced by MA [$F(2, 14) = 5.509$, $p<0.05$] and a significant interaction between dose and lever was observed [$F(2, 14) = 4.897$, $p<0.05$]. Simple contrasts revealed that both doses of MA significantly increased active lever responding compared to vehicle priming injections ($p<0.05$).

3.3. Experiment 2: GBR12909 induced drug-seeking

Fig. 3 shows the effect of GBR 12909 on drug-seeking. GBR 12909 produced a dose-dependent increase in drug-seeking behavior [$F(2, 6) = 14.229$, $p<0.05$], and an interaction between GBR12909 dose and lever was also produced [$F(2, 6) = 20.973$, $p<0.05$]. Simple contrasts confirmed that the 10.0 mg/kg dose produced the increase in active lever responding ($p<0.05$).

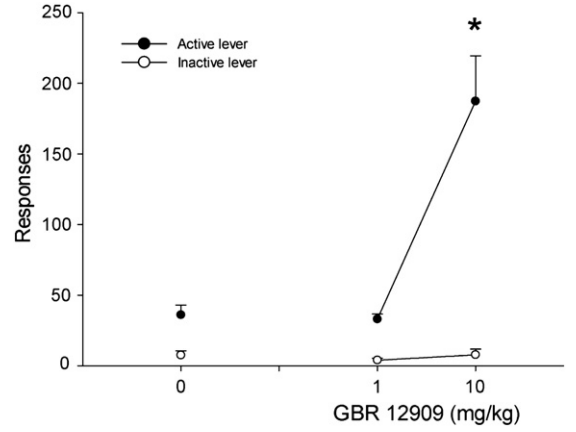

Fig. 3. Mean (+SEM) number of responses during reinstatement tests as a function of priming injections of GBR 12909 ($n = 4$). *Significantly different from vehicle ($p<0.05$).

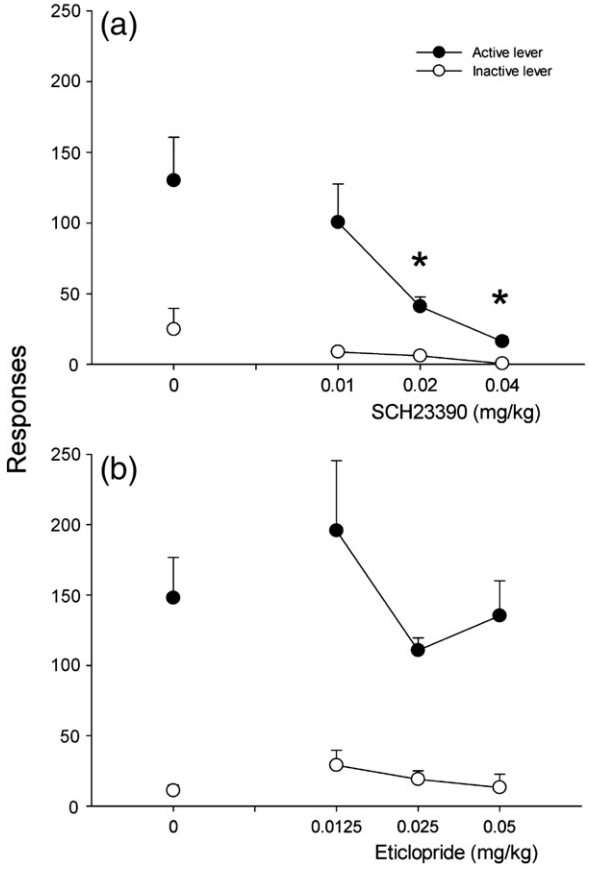

Fig. 4. Mean (+SEM) number of responses during drug-seeking tests as a function of (a) SCH 23390 (n = 5), and (b) eticlopride pre-treatment (n = 4). *Significantly different from vehicle ($p<0.05$).

3.4. Experiment 3: effects of D1 and D2 antagonists on MA induced drug-seeking

Fig. 4 shows the effect of pre-treatment with D1- and D2-like antagonists on drug-seeking produced by MA (2.0 mg/kg, IP). ANOVA revealed that MA-produced drug-seeking was dose-dependently attenuated by SCH 23390 [$F(3, 12) = 9.145$, $p<0.05$]. Simple contrasts confirmed that the 0.02 and 0.04 mg/kg doses significantly decreased drug-seeking behavior ($p<0.05$). Pre-treatment with eticlopride, however, failed to significantly decrease drug seeking [$F(3,9) = 1.168$, $p>0.05$].

4. Discussion

The results of this study support the idea that dopaminergic mechanisms are important for MA seeking, and further suggest an important role of D1-, but not D2-like receptor mechanisms. During training, rats received substantial exposure to self-administered MA (32.4–93.9 mg/kg over 32 days). When MA was replaced with saline and the drug-paired light stimulus was omitted, responding decreased to less than 20% of baseline levels. Drug-seeking was produced by the DA uptake inhibitor, GBR 12909, and by MA.

SCH 23390 decreased MA-produced drug-seeking. A large number of other studies have reported similar effects of SCH 23390, and other D1-like antagonists (Alleweireldt et al., 2002; Anderson et al., 2003; Hiranita et al., 2010; Khroyan et al., 2000; Shaham and Stewart, 1996; Weissenborn et al., 1996), consistent with an important role of this receptor in drug-seeking behavior. SCH 23390 is also an agonist at the 5-HT2c receptor, but the doses required are 10-fold higher than those required for D1-like receptor blockade (Bourne, 2001; Millan et al., 2001). It is also possible that the attenuation of the drug-seeking effect reflects a non-specific generalized decrease in the ability to perform the lever press response. This seems unlikely, however, as we have previously demonstrated an increase in responding maintained by some doses of cocaine (Brennan et al., 2007) and MDMA (Daniela et al., 2004) self-administration following pre-treatment with 0.02 mg/kg SCH 23390.

Eticlopride failed to significantly alter the drug-seeking response. This finding is unusual since many other studies have shown an attenuation of drug-seeking behavior following administration of eticlopride and other D2-like receptor antagonists (Khroyan et al., 2000; Schenk and Gittings, 2003; Self, 1998, 2004; Self et al., 1996; Shaham and Stewart, 1996). For example, cocaine-seeking behavior in monkeys was dose dependently attenuated by pretreatment with the D2-like antagonists eticlopride and nemonapride (Khroyan et al., 2000), and in rats by pretreatment with the novel D1 agonist/D2 antagonist LEK-8829 (Milivojevič et al., 2004). Reinstatement of heroin-seeking behavior was also attenuated by the D2-like antagonist, raclopride, suggesting that D2-like receptors contribute to heroin-induced relapse (Shaham and Stewart, 1996). Furthermore, following cocaine self-administration under almost identical protocols to the present study, eticlopride attenuated cocaine-, WIN 35,428- (Schenk and Gittings, 2003) and caffeine-produced drug-seeking (Green and Schenk, 2002). It is unlikely that the lack of eticlopride effect seen here is due to an inadequate dose as the current doses are comparable to effective doses used in cocaine-primed reinstatement studies (e.g. Khroyan et al., 2000; Schenk and Gittings, 2003). We did not test higher doses because they have been shown to produce non-specific generalized decreases in motor activity (Green and Schenk, 2002; Schenk and Gittings, 2003). The failure of eticlopride to attenuate drug-primed reinstatement of MA-seeking is consistent with the finding that eticlopride failed to alter the dose–response curve for MA self-administration (Brennan et al., 2009), and further suggests that D2-like receptor mechanisms are not critical for the reinstatement of MA-seeking behavior.

The failure of eticlopride to alter drug-seeking may be explained by the novel effects of repeated MA exposure on DA neurotransmission and D2-like receptor mechanisms. Reduced levels of DA and D2-like receptor availability have been consistently reported in human drug abusers, including those with a history of MA abuse (Lee et al., 2009; Martinez et al., 2009; Volkow et al., 2001). Rodents self-administering MA for 6 h/day presented no changes in monoamine tissue levels in prefrontal cortex or nucleus accumbens (Schwendt et al., 2009), transient reductions in striatal DA levels (Brennan et al., 2010), and a persistent decrease in DA transporter (DAT) protein levels in prefrontal cortex and dorsal striatum (Schwendt et al., 2009). However, increasing session duration to 15 h/day produced transient changes in NE and 5-HT levels, with persistent dose-dependent reductions in DA, DAT, and tyrosine hydroxylase levels in the striatum and cortex (Krasnova et al., 2010). More extensive testing, using longer self-administration sessions, may therefore reveal neurochemical consequences that are not apparent following shorter sessions, as in the current study. Reduced levels of both D1- and D2-like receptor availability have also been demonstrated in laboratory rodents following experimenter administered MA infusions, but there were greater reductions in D2-like receptor binding densities (Segal et al., 2005). Self-administered MA, under protocols almost identical to the current study, also produced more substantial decreases in D2-like receptor binding (Stefanski et al., 1999). Greater reductions in D2-like receptor binding densities, as a function of self-administered MA exposure, may explain the preferential effect of SCH 23390 on MA-seeking behavior.

Comparable effects have not always been observed following self-administration of other drugs. Following cocaine exposure, for example, the findings have been somewhat equivocal, and decreases (Nader et al., 2002), increases (Peris et al., 1990), or no change in D2-

like receptor binding (Wallace et al., 1996) have been reported. Importantly, exposure to self-administered cocaine (2–6 h sessions) failed to produce persistent changes in D2-like receptor binding densities (Ben-Shahar et al., 2007; Briand et al., 2008; Laurier et al., 1994; Stefanski et al., 2007). This might explain why drug-seeking following cocaine self-administration is susceptible to pharmacological antagonism of both D1- and D2-like receptor mechanisms whereas drug-seeking following MA self-administration was susceptible to pharmacological antagonism of only D1-like receptors.

These findings are consistent with the idea that MA self-administration may produce neuroadaptations not seen following self-administration of other drugs of abuse. We have previously demonstrated that eticlopride pre-treatment also failed to alter MA self-administration (Brennan et al., 2009). This, together with the present results, suggests that under the current protocols, D2-like receptor mechanisms may undergo novel neuroadaptations as a function of MA self-administration rendering this behavior more susceptible to pharmacological manipulations of D1-like receptor mechanisms. On the basis of these data, we hypothesize that reinstatement of MA-seeking behavior becomes dissimilar from other drugs of abuse, relying more on DA D1-, than D2-like receptor mechanisms.

Acknowledgements

Funding was provided by the Neurological Foundation of New Zealand, and the authors greatly acknowledge the technical assistance of Richard Moore, and Dr Katie Brennan.

The authors declare no conflicts of interest.

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