Neurobiology of Learning and Memory 95 (2011) 473–483

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

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

The effects of binge MDMA on acquisition and reversal learning in a radial-arm maze task

C. Kay, D.N. Harper *, M. Hunt

School of Psychology, Victoria University of Wellington, New Zealand

ARTICLE INFO

Article history:
Received 8 December 2010
Revised 10 February 2011
Accepted 22 February 2011
Available online 1 March 2011

Keywords:
MDMA
Ecstasy
Working memory
Reference memory
Binge
Radial arm maze

ABSTRACT

The current study used the partially-baited radial-arm maze paradigm to study the effects of a single-treatment high-dose exposure ('binge') to MDMA (±3,4-methylenedioxymethaphemtamine or 'Ecstasy') on memory task acquisition. Sprague–Dawley rats were administered a binge dose (4 × 10 mg/kg) of MDMA and their ability to subsequently acquire the radial-arm maze task was compared against saline controls. The MDMA-treated rats were significantly slower to learn the task and made more reference memory errors than the controls. Working memory function was found to be relatively unimpaired. Following a reversal of task rules the MDMA-treated rats were again significantly slower to acquire the appropriate rule despite having eventually achieved a similar level of overall performance as control rats. However evidence of drug tolerance was found when all rats were challenged with an acute low dose of MDMA (1 × 4.0 mg/kg) because the binge MDMA rats were relatively less impaired. Therefore, although binge treated MDMA rats were able to achieve very accurate performance equivalent to the controls they took significantly longer to do this and were less able to adapt their behavior to a change in task rules. In addition the binge treated MDMA rats displayed tolerance to acute MDMA exposure. These findings are consistent with the possibility that human Ecstasy users may show deficits in acquiring information and may experience deficits in cognitive flexibility as well as developing tolerance to the drug with repeated exposure.

1. Introduction

Although recreational MDMA (±3,4-methylenedioxymethaphemtamine or 'Ecstasy') use causes a range of positive behavioral and emotional changes, users also demonstrate general mental confusion (Davison & Parrott, 1997) and significant impairments on a variety of cognitive tasks (Heffernan, Jarvis, Rodgers, Scholey & Ling, 2001). As well as general memory deficits (Rodgers, 2000) there are more specific areas of cognitive function that are impaired with Ecstasy use such as the ability to learn and recall verbal information (e.g., Bolla, McCann, & Ricaurte, 1998; McCardle, Luebbers, Carter, Croft, & Stough, 2004; Morgan, McFie, Fleetwood, & Robinson, 2002; Parrott & Lasky, 1998; Rodgers, 2000; Smith, Tivarus, Campbell, Hillier, & Beversdorf, 2006). Ecstasy use has also been associated with impairments in various tasks that assess executive functioning (e.g., Wareing, Fisk, & Murphy, 2000; Montgomery, Fisk, & Newcombe, 2005; Zakzanis & Young, 2001) including tasks that are used to assess working memory (Morgan et al., 2002; VonGeusau, Stalenhoef, Huizinga, Snel, & Ridderinkhof, 2004; Wareing, Murphy, & Fisk, 2004).

However as noted by a number of researchers the findings from Ecstasy users are confounded by a number of variables such as the purity of Ecstasy tablets, the amount used, pre-existing cognitive impairments, the self report measures used and polydrug use. These factors make determining whether MDMA actually causes cognitive impairments difficult and they also make establishing the exact nature of the cognitive impairments seen in Ecstasy users difficult to ascertain. Animal studies help resolve these issues as they provide a much greater degree of experimental control.

Many different kinds of tasks have been used to assess the effects of chronic and binge MDMA administration on cognition in animal models. Although acute MDMA exposure has been found to impair performance on delayed matching to sample (DMTS) tasks in a variety of species (Frederick, Gillam, Allen, & Paule, 1995; Harper, Hunt, & Schenk, 2006; Harper, Wisnewski, Hunt, & Schenk, 2005; LeSage, Clark, & Poling, 1993; Taffe et al., 2001), studies that have examined ongoing performance changes as a result of binge or chronic MDMA exposure have sometimes failed to produce evidence of impairments on these tasks (Frederick et al., 1995, 1998; LeSage et al., 1993; Taffe et al., 2001). However, the absence of an ongoing impairment is not universal. For example, Marston, Reid, Lawrence, Olverman, and Butcher (1999) found a binge regime of MDMA impaired DNMTP performance during drug administration days and this deficit did not improve 16 days post

* Corresponding author. Address: School of Psychology, Victoria University of Wellington, PO Box 600, Wellington, New Zealand.
E-mail address: david.harper@vuw.ac.nz (D.N. Harper).

1074-7427/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2011.02.010

drug treatment suggesting it had a harmful long-term effect on memory. Therefore the evidence that chronic or binge MDMA exposure produces memory deficits in DMTS-type tasks is mixed, with the majority of studies failing to produce evidence of impairment.

Various maze tasks have been used to assess the effects of chronic and binge doses of MDMA on cognition. Some early studies found that despite binge MDMA treatments producing significant reductions in brain 5-HT they failed to produce evidence of cognitive impairments as assessed using a complex 24 arm maze task (Slikker et al., 1989) or a simpler T-maze task (Ricaurte et al., 1993). However more consistent evidence that MDMA exposure may affect spatial memory comes from other maze tasks such as the Cincinnati water maze (multiple T-maze). Both binge (Skelton et al., 2008) and chronic (Broening, Morford, Inman-Wood, Fukumura, & Vorhees, 2001; Skelton, Williams, & Vorhees, 2006; Skelton et al., 2009; Williams et al., 2003) regimes of MDMA have been shown to impair performance on this maze task indicating MDMA exposure appears to impair spatial memory and path integration processes (Skelton et al., 2008).

In addition, research utilizing the Morris water maze, which is one of the most commonly used mazes to assess spatial memory (D'Hooge and De Deyn, 2001), has found evidence that MDMA exposure can produce deficits in cognitive performance. Researchers have examined the developmental impact of MDMA by administering chronic regimes of MDMA to adolescent rats and examining their ability to acquire water maze tasks in adulthood. These studies have typically found that chronic MDMA exposure impairs performance on water maze tasks (Broening et al., 2001; Skelton et al., 2006, 2009; Vorhees, Reed, Skelton, & Williams, 2004; Williams et al., 2003). Binge MDMA treatments administered in adult rats have also been shown to produce impairments in Morris water maze performance (Robinson, Castaneda, & Whishaw, 1993; Sprague, Preston, Leifheit, & Woodside, 2003; Able, Gudeksky, Vorhees & Williams, 2006; Skelton et al., 2008). Interestingly when examining the different types of Morris water maze tasks it has been found that both binge and chronic MDMA exposure impairs performance on the standard water maze task that it used to assess reference memory processes (Lindner, Balch, & Vandermaelen, 1992) but leaves other forms of the task that assess working memory (Vorhees et al., 2004) and cued memory intact (Broening et al., 2001; Vorhees et al., 2004; Williams et al., 2003). Thus there is evidence that both chronic and short-term binge regimes of MDMA impair reference memory processes more than other memory processes. However it should be noted that the Morris water maze has a potential confound in that it uses the aversive stimulus of being placed in water to motivate the escape behavior of rats. This may be problematic because chronic MDMA exposure had been shown to reduce anxiety in rats (Mechan et al., 2002).

The partially baited radial arm maze paradigm is a particularly useful paradigm as it enables both reference and working memory processes to be examined simultaneously (Olton & Papas, 1979). Using this paradigm the previous research examining the binge and chronic effects of MDMA on Morris water maze performance can be extended by allowing working and reference memory processes to be investigated using the same procedure. To date the only study that has used this apparatus in chronic MDMA research was conducted on rats that were prenatally treated with MDMA and this produced no effect on maze performance in the offspring of these rats when tested in adulthood (Thompson et al., 2009). However, this finding does not answer whether MDMA exposure would affect radial maze performance in rats who are directly administered the drug rather than being exposed via their pregnant mothers.

There is also some question as to the longevity of the impairments seen in MDMA-induced cognitive deficits. While there have been instances where the deficits seen after binge MDMA exposure have been transient (Robinson et al., 1993) there is also some evidence that chronic and binge MDMA exposure have produced more long-term cognitive deficits which remain several weeks after drug exposure (Broening et al., 2001; Skelton et al., 2006; Sprague et al., 2003; Vorhees et al., 2004; Williams et al., 2003; Able et al., 2006; Skelton et al., 2008, 2009). Also, in addition to learning impairments, there is evidence that MDMA exposure may impede the ability of subjects to adapt their behavior to changing consequences. For example the Wisconsin Card Sorting Task (WCST) utilizes a constant changing of task rules that is used to accesses cognitive flexibility and it has been found that Ecstasy users are impaired on this task (Smith et al., 2006; VonGeusau et al., 2004). Similarly tasks that assess associative learning have been found to be impaired due to perseverative responding in Ecstasy users (Montgomery et al., 2005) and Ecstasy use has also been associated with task switching deficits using a modified Stroop task (Lamers, Bechara, Rizzo, & Ramaekers, 2006; Dafters, 2006). Within the animal literature there is also evidence that reversal learning is impaired after MDMA exposure where MDMA treated animals have shown deficits during reversal phases of the Morris water maze (Skelton et al., 2006; Skelton et al., 2008, 2009; Williams et al., 2003) where after initial task acquisition the position of the platform is moved (Morris, 1984).

Another issue of interest in MDMA research is whether Ecstasy exposure results in drug *tolerance* versus *sensitization*. Ecstasy users have reported having to increase the amount of the drug they take to experience the positive effects of the drug (Parrott, 2001) indicating they become tolerant to the effects of the drug. However, animal studies have found mixed results where some studies have found evidence of drug tolerance occurring after repeated exposure to the drug (Brennan & Schenk, 2006; Frederick & Paule, 1997; Frederick et al., 1995, 1998; LeSage et al., 1993; Marston et al., 1999; Piper, Vu, Safain, Oliver, & Meyer, 2006; Shankaran & Gudelsky, 1999) and others have reported repeated MDMA exposure produces behavioral sensitization (Kalivas, Duffy, & White, 1998; Li, Marek, Vosmer, & Seiden, 1989; Modi, Yang, Swann, & Dafny, 2006; Moyano, Del Rio, & Frechilla, 2005; Spanos & Yamamoto, 1989). The reasons why such conflicting findings as to whether repeated MDMA exposure results in tolerance or sensitization are unclear. However, Brennan and Schenk (2006) suggested that repeatedly administering low doses of MDMA may result in sensitization developing to the effects of MDMA while tolerance may develop following the administration of large chronic or binge doses.

Therefore the present study examined the effect of a binge regime of MDMA on acquisition in the partially baited radial arm. It was hypothesized that MDMA-treated rats would be impaired in their ability to adapt their behavior compared to saline controls which would be evident by MDMA-treated rats acquiring the new task more slowly than controls during acquisition and reversal phases. Acute doses of MDMA (4 mg/kg) and saline were also administered during acquisition and reversal training in order to examine whether behavioral tolerance would be evident in rats that were previously exposed to MDMA.

2. Materials and methods

2.1. Subjects

The subjects were twenty white male Sprague–Dawley rats that were approximately three to 4 months old at the beginning of the study. The rats were bred in-house and were caged individually. They were experimentally naïve at the beginning of the study and were kept at 85–90% (between 218 and 324 grams) of their