Pharmacology, Biochemistry and Behavior 116 (2014) 9–15

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

A 3-lever discrimination procedure reveals differences in the subjective effects of low and high doses of MDMA

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ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form 1 November 2013
Accepted 8 November 2013
Available online 16 November 2013

Keywords:
MDMA
D-Amphetamine
SCH23390
Dopamine
Drug discrimination

ABSTRACT

Drug discrimination studies have suggested that the subjective effects of low doses of (±)3,4-methylenedioxymethamphetamine (MDMA) are readily differentiated from those of D-amphetamine (AMPH) and that the discriminative stimulus properties are mediated by serotonergic and dopaminergic mechanisms, respectively. Previous studies, however, have primarily examined responses to doses that do not produce substantial increases in extracellular dopamine. The present study determined whether doses of MDMA that produce increases in synaptic dopamine would also produce subjective effects that were more like AMPH and were sensitive to pharmacological manipulation of D1-like receptors. A three-lever drug discrimination paradigm was used. Rats were trained to respond on different levers following saline, AMPH (0.5 mg/kg, IP) or MDMA (1.5 mg/kg, IP) injections. Generalization curves were generated for a range of different doses of both drugs and the effect of the D1-like antagonist, SCH23390 on the discriminative stimulus effects of different doses of MDMA was determined. Rats accurately discriminated MDMA, AMPH and saline. Low doses of MDMA produced almost exclusive responding on the MDMA lever but at doses of 3.0 mg/kg MDMA or higher, responding shifted to the AMPH lever. The AMPH response produced by higher doses of MDMA was attenuated by pretreatment with SCH23390. The data suggest that low doses and higher doses of MDMA produce distinct discriminative stimuli. The shift to AMPH-like responding following administration of higher doses of MDMA, and the decrease in this response following administration of SCH23390 suggests a dopaminergic component to the subjective experience of MDMA at higher doses.

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1. Introduction

The primary pharmacological effect of drugs of abuse can vary substantially but they share the ability to increase dopamine (DA) neurotransmission (Di Chiara and Imperato, 1988; Di Chiara et al., 2004). Amongst the various amphetamines, the pharmacology of 3,4-methylenedioxymethamphetamine (MDMA) differs because effects are produced preferentially on the serotonergic system. Thus, while both amphetamine (AMPH) and MDMA increase synaptic DA by inhibiting the DA transporter and stimulating release, AMPH releases DA (EC_{50} = 25nM) around 11 times more potently than racemic MDMA (EC_{50} = 278nM). In contrast, MDMA is much more potent than AMPH in terms of serotonin release (around 24 times more potent; EC_{50} = 74nM vs. EC_{50} = 1,765nM); see Baumann et al. (2007). Thus, following acute administration, AMPH produces a relatively greater increase in synaptic DA, whereas MDMA produces a relatively greater increase in synaptic serotonin (Baumann et al., 2008).

These neurochemical effects are often reflected in different behavioral responses, including the discriminative stimulus properties, of AMPH and MDMA. For example, novel DA agonists have been shown to substitute for a previously trained AMPH stimulus (Callahan et al., 1991; van Groll and Appel, 1992), whereas serotonin agonists produce generalized responding to a previously trained MDMA stimulus (Schechter, 1986, 1998; Goodwin and Baker, 2000). Furthermore, DA antagonists can attenuate the discriminative stimulus properties of AMPH (Callahan et al., 1991; van Groll and Appel, 1992) whereas serotonin antagonists can attenuate the discriminative stimulus properties of MDMA (Schechter, 1988; Glennon et al., 1992; Goodwin et al., 2003; Smithies and Broadbear, 2011). It should be noted, however, that some studies have found that AMPH can fully or partially substitute for MDMA, suggesting a common neurochemical mechanism (Glennon and Misenheimer, 1989; Oberlender and Nichols, 1988; Schechter, 1989) but these results have not been replicated in other studies (Baker et al., 1995; Baker and Makhay, 1996; Goodwin et al., 2003). Thus, the bulk of the available data suggests separate but overlapping interoceptive cues following AMPH and MDMA, with the former being mediated by dopaminergic and the latter by serotonergic mechanisms.

The most convincing demonstration of the different subjective effects for MDMA and AMPH comes from studies that have used a three-lever discrimination task because in these studies the subject learns to discriminate MDMA from AMPH and saline simultaneously. One such study initially trained rats to discriminate between 1.0 mg/kg

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0091-3057/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pbb.2013.11.011

AMPH, 1.5 mg/kg MDMA and vehicle (Goodwin and Baker, 2000). Drug-appropriate responding increased in a dose-dependent manner up to the training dose but there was no significant degree of inappropriate MDMA-lever or AMPH-lever responding when the other target drug was given. Serotonin agonists (LSD, fenfluramine and DOM) fully or partially substituted for MDMA, while cocaine produced AMPH-appropriate responding. These results indicated that the subjective effects of AMPH and MDMA are clearly distinguishable, at least when these doses are used, and that these effects are due to different neurochemical mechanisms.

Although a role of serotonin in the discriminative stimulus effects of MDMA has been demonstrated in both 2- and 3-lever tasks, the role that DA plays remains relatively unexplored. Recent evidence indicated that MDMA-induced impairments in a conditional discrimination task were ameliorated by pre-treatment with the D1 antagonist, SCH23390 (Harper, 2011). Similarly, in a previous 2-lever discrimination study, the ability to discriminate the (+) isomer of MDMA from saline was significantly reduced following prior administration of SCH23390 (Bubar et al., 2004; Harper et al., 2011), but not the D2 antagonist, eticlopride (Bubar et al., 2004). This might reflect the more potent dopaminergic effects of this isomer. The role played by different dopamine receptors in the discriminative stimulus properties of racemic MDMA have not, however, been directly determined.

The dose of MDMA that is generally used in drug discrimination studies (1.5 mg/kg) is, relatively low compared to doses that are required to produce other DA-mediated behavioral responses. When the dose of MDMA is increased, however, responses that are more consistent with dopaminergic effects are sometimes produced. For example, Kueh and Baker (2007) showed that at doses that did not disrupt overall responding neither cocaine nor amphetamine substituted for MDMA in rats trained to discriminate 1.5 mg/kg MDMA from saline. However, in rats trained to discriminate cocaine from saline, although a low dose of 1.5 mg/kg MDMA failed to substitute for cocaine, a higher dose of 3.0 mg/kg showed partial substitution. The MDMA drug discrimination studies are, therefore, usually biased towards observing effects that are mediated by serotonin (i.e., low doses). Because higher doses of MDMA that produce greater increases in DA are rarely tested, the idea that the discriminative stimulus effects of at least some doses of MDMA have a DA component has not yet been adequately tested.

Higher doses of MDMA are required to produce increases in synaptic DA that are comparable to the doses of AMPH (2.0 mg/kg), cocaine (10.0 mg/kg) and methamphetamine (1.0 mg/kg) that have typically been used as discriminative stimuli in drug discrimination studies (see Schenk, 2011 for review). A dose of 1.0 or 2.0 mg/kg AMPH that is typically used in drug discrimination studies increases synaptic DA by between 500 and 2000%, depending on the study (see for example, Di Chiara et al., 1993; Shoblock et al., 2003; Ren et al., 2009). Importantly, AMPH has been shown to be much more potent than MDMA in this regard (Yamamoto et al., 1995; Bankson and Yamamoto, 2004; Kankaanpää et al., 1998; Kurling et al., 2008). It might therefore not be surprising that AMPH and other drugs that produce discriminative stimulus properties via dopaminergic mechanisms fail to substitute for the MDMA stimulus in rats trained to discriminate a low dose of MDMA from saline. At such a low dose MDMA is likely to produce distinct stimulus properties that are readily discriminated from the effects of AMPH. What is not known is whether higher doses of MDMA (which will produce a more prominent DA response) will also produce a different profile of subjective effects compared to relatively lower doses.

A recent study suggested, in fact, that a critical synaptic level of DA was required for drugs to substitute for a methamphetamine stimulus (Desai et al., 2010). Their study showed that doses of drugs that produced increases in DA overflow of about 200–400% fully substituted for methamphetamine; whereas lower doses failed to substitute. Accordingly, a higher dose of MDMA that produces a comparable increase in synaptic DA might also be required in order for a DA mediated response to be produced.

In order to assess this possibility, the current study measured the discriminative stimulus effects of different doses of MDMA (0.5–4.5 mg/kg) and AMPH (0.5–1.5 mg/kg) and assessed the effect of the D1-like antagonist, SCH23390, using a 3-lever discrimination procedure. We expected that the 3-way discrimination would be readily demonstrated following lower doses of MDMA but that a shift to AMPH-like responding would be produced following administration of higher dose that produced a more prominent dopaminergic response. We also expected that effects of the higher, but not the lower, doses of MDMA would be susceptible to effects of the dopamine antagonist.

A second issue examined in the current study was whether the subjective effects of MDMA differed for male versus female rats. Several studies have indicated that male and female rats are differentially sensitive to the acute effects of MDMA in various aspects of spontaneous and locomotor activity (e.g., Pálenícek et al., 2007), which has been attributed to the increased reactivity of serotonergic and dopaminergic systems in female rats to MDMA exposure (Pálenícek et al., 2005). Similarly, Broadbear et al. (2011) found some evidence that female rats were more sensitive to MDMA in a drug discrimination procedure in that they exhibited a greater propensity to respond on the MDMA-appropriate lever at lower doses of MDMA relative to male rats. However, Broadbear et al. only examined one dose of MDMA (1.5 mg/kg) and evidence exists that male and female rats do not differ in their ability to discriminate cocaine from saline or in terms of tendency to substitute AMPH for cocaine, even at doses that produce significantly greater locomotor responses in females versus males (Craft and Stratmann, 1996). Thus, a supplementary question in the current study was whether male versus female rats would differ in terms of discrimination performance across a range of MDMA doses.

2. Materials and methods

2.1. Animals

Subjects were 14 experimentally naive Norway Hooded rats. Rats had previously been exposed to operant training on a single lever in an undergraduate lab and were drug naïve. Of the 14 rats, 8 were female and remaining 6 were male. The female rats weighed between 210 and 260 g and the male rats weighed between 320 and 400 g and all rats were approximately 6 months old at the start of training. Subjects were housed in pairs in a room maintained on a 12-h light (0700–1900)/12 h dark cycle and kept at temperatures between 20–22° C. Subjects were allowed free access to water while commercial rat food was rationed to maintain body weights of 85–90% of free feeding weights. The animals were cared for, and the research conducted, using protocols approved by the Victoria University of Wellington Animal Ethics Committee.

2.2. Apparatus

All training and testing sessions took place in 14 commercially available rodent operant chambers (ENV221M: MED Associates Inc., Georgia, VT) containing three retractable levers. A sugar pellet dispenser was located at the center of the front panel, while one lever was situated to the right and one to the left of it, respectively. The third lever was located at the center of the back panel of the operant chamber. Standard 100 mA white lights were situated above every lever. MED-PC ® IV instrumentation and software were used to run experimental events and for data collection. Sugar pellets (45 mg Dustless Precision Pellets, product number F0042) were obtained from Bio Serv® (Frenchtown, NJ).

2.3. Drugs

Racemic-MDMA hydrochloride was obtained from the Institute of Environmental Science and Research (Porirua, New Zealand),

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