Evaluating the Contribution of Serotonin Receptor Subtypes and 'Binge' 3,4-Methylenedioxymethamphetamine (MDMA) Exposure to the Discriminative Stimulus Effects of MDMA in Rats

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INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA; 'Ecstasy') shares psychoactive effects with drugs that possess stimulant (e.g. amphetamine, the effects of which are primarily dopaminergic) and hallucinogenic properties (e.g. LSD, which has serotonergic effects) [1]. The majority of MDMA's distinctive effects as well as its toxicity have been linked to its actions on serotonergic neurotransmission [2]. One way in which MDMA's serotonergic effects can be studied is to train rats to distinguish dopaminergic stimulant effects from mood and perception-altering serotonergic effects using a three-way drug discrimination paradigm [3].

METHOD

Male and female Sprague Dawley rats were trained to reliably differentiate between d-amphetamine (0.75mg/kg), MDMA (1.5mg/kg) and saline. The contributions of serotonin$_{1A}$ and serotonin$_{2A/C}$ (5-HT$_{1A}$ and 5-HT$_{2A/C}$) receptors to MDMA's interoceptive effects were then evaluated. This was done both before and after the rats were exposed to an MDMA 'binge' (3 x 10mg/kg MDMA injections given at two hourly intervals) to determine whether a reportedly neurotoxic dosing regimen [4] would disrupt the interoceptive cues of MDMA.

Table 1. Frequency and Percent of Choice of MDMA, AMP, and SAL Levers for First Completed Fixed Ratio (FR=10 Lever Presses) in Response to MDMA (1.5mg/kg) Alone or in Combination with Ritanserin (1.5mg/kg and 3mg/kg;) or WAY 100,635 (1mg/kg)

Lever	MDMA (n=10)		+ Ritanserin (n=8)		+ WAY100,635 (n=10)	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
MDMA	10	100	5	62.5	8	80
AMP	0	0	0	0	0	0
SAL	0	0	3	37.5	2	20

Table 2. Frequency and Percent of Choice of MDMA, AMP, and SAL Levers for First Completed Fixed Ratio (FR=10 Lever Presses) in Response to MDMA (1.5mg/kg) Administration Post Binge

Lever (n=6)	Post-Binge Day 2		Post-Binge Day 5		Post-Binge Day 8	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
MDMA	3	50	4	66.7	4	66.7
AMP	1	16.7	0	0	0	0
SAL	2	33.3	2	33.3	2	33.3

RESULTS

Blockade of 5-HT$_{1A}$ or 5-HT$_{2A/C}$ receptors, *via* administration of WAY 100,635 (1 mg/kg) or ritanserin (1.5 and 3 mg/kg), significantly disrupted MDMA-appropriate

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responding, as evident from the variability in the training drug-appropriate lever on which the first response ratio was completed (see Table **1**). Binge MDMA exposure also resulted in selective disruption to the MDMA training cue during the subsequent 8 days (see Table **2**). Once the discrimination had recovered, repeating the antagonist tests revealed that the disruptions by the 5-HT_{1A} and 5-$HT_{2A/C}$ receptor antagonists to MDMA's discriminative cues were not significantly different to what was measured prior to the 'binge'.

DISCUSSION

Co-administration of MDMA with 5-HT_{1A} and 5-$HT_{2A/C}$ antagonists, WAY and ritanserin interrupted the interoceptive cues that rats used to discriminate MDMA from amphetamine, which is consistent with findings from other studies [3,5]. This implies that for some rats the discriminative stimulus effects of MDMA were mediated by 5-HT_{1A} and/or 5-$HT_{2A/C}$ mechanisms of action. The MDMA 'binge' dosing regimen resulted in a transient reduction in MDMA-appropriate lever responding that continued to be disrupted in a third of subjects at least 8 days later (persisting for 16 and 69 days in the remaining 2 rats). This suggests that MDMA's discriminative stimulus effects were disrupted following high-dose MDMA administration, consistent with previous evidence of alterations in 5-HT neurotransmission after MDMA exposure [2]. The discrimination did recover over time however, supporting the suggestion that the neuronal effects of high-dose exposure may be transient [6]. Binge administration did not influence the contributions of 5-HT_{1A} and5-$HT_{2A/C}$ receptor activation to MDMA's discriminative cues, which provides preliminary evidence to suggest that the recovered 'discrimination' was based on the same interoceptive cues as the pre-binge discrimination.

CONCLUSION

This study provides support for the importance of 5-$HT_{1A,\ 2A/C}$ mediated cues in the discriminative, and by extension behavioural and neurotoxic effects of MDMA, and suggests that MDMA's discriminative stimulus effects are only temporarily disrupted following high-dose MDMA exposure.

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