Introduction

Experimental investigations into the behavioral and neurochemical effects of illicit β-ketophenylethylamines (synthetic cathinones, “bath salts”) has increased in recent years. Two cathinone derivatives in particular, MDPV and methedrone (4-MMC), have received a considerable amount of research attention given their relative popularity among users at the turn of the 21st century. Researchers investigating MDPV and 4-MMC have devoted much of their attention toward evaluating the drugs’ reinforcing efficacy, rewarding effects, receptor binding profiles, and effects on ambulatory responses.

There exist few published studies that have evaluated the discriminable stimulus effects of MDPV and 4-MMC using rodent drug discrimination procedures. To date, only two of these previous experiments included doses of MDPV or 4-MMC as the training drug (Fantegrossi et al., 2013; Varner et al., 2013).

The present study assessed the discriminable stimulus effects of MDPV or 4-MMC in male rats trained to discriminate 0.3 mg/kg MDPV or 1.0 mg/kg 4-MMC from saline. In this experiment, several prototypical drugs of abuse that produce effects on monoamine functioning were evaluated using stimulus generalization tests.

Methods

Subjects: Sixteen male Sprague-Dawley rats (350-430 g) were singly housed with ad libitum access to water and maintained at 85-90% of free-feeding body weights.

Apparatus: Training and test sessions were conducted in eight standard operant conditioning chambers equipped with retractable levers and housed within sound-attenuating compartments (Med Associates, St. Albans VT).

Procedures: Rats were trained to discriminate intraperitoneal (i.p.) injections of 0.3 mg/kg MDPV (n=8) or 1.0 mg/kg 4-MMC (n=8) from vehicle (saline) under an FR 20 schedule of food reinforcement. Criteria for discrimination acquisition were a minimum of 80% correct lever responding prior to completion of the first FR and for the total session for at least 8 consecutive training sessions. When these criteria were met, stimulus generalization was assessed with the following test compounds:

- MDPV (0 – 3.0 mg/kg)
- 4-MMC (0 – 10.0 mg/kg)
- d-amphetamine (0 – 1.0 mg/kg)
- (+)-methamphetamine (0 – 3.0 mg/kg)
- cocaine (0 – 10 mg/kg)
- MDMA (0 – 3.0 mg/kg)
- LSD (0 – 0.1 mg/kg)
- fenfluramine (0 – 3.0 mg/kg)

All drugs were delivered via intraperitoneal injection; pre-session injection interval 15 min. Data collection is ongoing for several stimulus generalization tests.

Results

Table 1: Sessions to Meet Discrimination Criteria for Each Training Group

<table>
<thead>
<tr>
<th>Mean ± SE</th>
<th>MDPV (n = 8)</th>
<th>4-MMC (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>20-54</td>
<td>20-69</td>
</tr>
</tbody>
</table>

Figure 1. Stimulus generalization test results with MDPV, 4-MMC, (+)-methamphetamine, d-amphetamine, cocaine, and fenfluramine in subjects trained to discriminate 0.3 mg/kg MDPV from saline. Percent drug-lever selection is displayed in upper graphs and response rate is displayed in lower graphs. Data points represent the group mean (± SE ± M).

Figure 2. Stimulus generalization test results with 4-MMC, MDPV, (+)-methamphetamine, d-amphetamine, cocaine, MDMA, LSD, and fenfluramine in subjects trained to discriminate 1.0 mg/kg 4-MMC from saline. Percent drug-lever selection is displayed in upper graphs and response rate is displayed in lower graphs. Data points represent the group mean (± SE ± M).

Conclusions

- There were no differences in establishing drug stimulus control in MDPV- versus 4-MMC-trained rats. This suggests the training doses of these drugs may be equieffective in producing salient discriminable cues.
- Full substitution was obtained with MDPV, 4-MMC, (+)-methamphetamine, d-amphetamine, cocaine, and tentatively fenfluramine in MDPV-trained rats. In addition, dose-dependent rate suppressant effects were observed for most test drugs.
- Full substitution was obtained with 4-MMC, MDPV, d-amphetamine, (+)-methamphetamine (in few subjects), cocaine, and MDMA in 4-MMC-trained rats. Similar to the MDPV-trained rats, most test drugs produced dose-dependent rate suppressant effects.
- Prototypical drugs of abuse that function as substrates or blockers for monoamine transporters may produce interoceptive effects similar to MDPV. In addition, the MDPV interoceptive cue may be mediated mostly by dopaminergic and noradrenergic activities, rather than by serotonergic mechanisms. Stimulus antagonism tests are warranted to further explore this possibility.
- Substrates or blockers for the dopamine and norepinephrine transporters produced full-substitution in 4-MMC-trained rats, similar to the results obtained in the MDPV-trained rats. Nevertheless, MDMA produced full substitution in the 4-MMC group, but not in the MDPV group. Serotonin release may contribute to the 4-MMC interoceptive cue. Stimulus antagonism tests are warranted to further explore this possibility.

References


Acknowledgements

This research was funded by the National Institutes of Health (R15DA038295). The National Institute on Drug Abuse Drug Control Supply Program provided drugs used in this study.