Published in final edited form as:

Drug Alcohol Depend. 2015 April 1; 149: 280–284. doi:10.1016/j.drugalcdep.2015.02.002.

Discriminative-Stimulus Effects of Second Generation Synthetic Cathinones in Methamphetamine-Trained Rats

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Abstract

Background—Synthetic cathinones are beta-ketophenethylamine analogs manufactured to avoid legal restrictions placed on illicit stimulants like methamphetamine. Regulating these “emerging” designer drugs requires scientific evidence of abuse potential.

Methods—The present study evaluated the discriminative-stimulus effects of three synthetic cathinones, recently identified in commercial and confiscated products, in male Sprague-Dawley rats trained to discriminate methamphetamine (1.0 mg/kg) from saline under a fixed-ratio (FR) 20 schedule of food delivery. Three synthetic cathinones, 4-methyl-N-ethylcathinone (4-MEC; 1.0–8.0 mg/kg), 4-methyl- α -pyrrolidinopropiophenone (4-MePPP; 4.0–16.0 mg/kg), and α -pyrrolidinopentiophenone (α -PVP; 0.25–2.0 mg/kg) were tested for their ability to substitute for methamphetamine.

Results—Full substitution for the training dose of methamphetamine occurred at the highest doses for both 4-MePPP and α -PVP, and 4-MEC did not substitute at any dose tested.

Conclusions—The present findings show that two synthetic cathinones, 4-MePPP and α -PVP, produced subjective effects similar to those of methamphetamine. The synthetic cathinone, 4-MEC, did not produce subjective effects similar to those of methamphetamine with the parameters used in the current experiment. Based on findings here and by others, these three compounds warrant further tests of abuse liability.

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Contributors: Authors W.L. Woolverton, and S.L. Huskinson designed the study. All authors participated in compiling and reviewing relevant literature. Authors J.E. Naylor and S.L. Huskinson collected, organized, and analyzed the data with mentorship from W.L. Woolverton and K.B. Freeman. Author B.E. Blough provided the synthetic cathinone compounds used in the study. Author J.E. Naylor wrote the first draft of the manuscript with mentorship from K.B. Freeman. All authors made significant contributions to the current draft, with the exception of Dr. Woolverton, who died before its preparation.

Conflict of Interest: Nothing declared

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Keywords

drug discrimination; synthetic cathinones; methamphetamine

1. Introduction

Synthetic cathinones are a class of beta-ketophenethylamine analogs that have behavioral effects similar to the prototypical stimulants, amphetamine and methamphetamine. A number of these drugs increase locomotor activity and fully substitute for amphetamine, cocaine, and methamphetamine (Dal Cason et al., 1997; Gatch et al., 2013; Glennon et al., 1995). A recent surge in abuse of synthetic cathinones has been driven by their commercial distribution at novelty stores and via the Internet (Leffler et al., 2014; Prosser and Nelson, 2012). Commercial availability of these drugs has been made possible by modifying their chemical structures in such a way that regulatory scheduling is avoided while the stimulant-like pharmacological and behavioral effects are left intact (Hill and Thomas, 2011). In recent years, several cathinone derivatives have been introduced in a serial fashion and have been categorized as first- and second-generation “bath salts”. Compounds assessed in the present study (under temporary Schedule I status) will be referred to as “second generation”: 4-methyl-N-ethylcathinone (4-MEC), 4-methyl-alpha-pyrrolidinopropiophenone (4-MePPP), and alpha-pyrrolidinopentiophenone (alpha-PVP).

Regulatory agencies require information on abuse potential to justify prohibitive scheduling of novel drugs. A constantly evolving drug class like synthetic cathinones presents a significant challenge to implementing timely regulation. Drug discrimination is one procedure used to characterize abuse potential of stimulants and other drugs (see Huskinson et al., 2014 for a recent review) and allows for comparisons to be made between the subjective effects of known drugs of abuse and novel drugs with unknown characteristics (Ator and Griffiths, 2003). Recent drug-discrimination studies suggest a high degree of similarity between the subjective effects of synthetic cathinones and existing stimulants, demonstrated by either full (80% drug-lever responses) or partial (20-79% drug-lever responses) substitution for the training drug (Fantegrossi et al., 2012; Gatch et al., 2014; Varner et al., 2013).

When a synthetic cathinone is used as the training drug, full or partial substitution of their discriminative-stimulus effects is seen with stimulants. Cocaine and methamphetamine partially substituted for mephedrone, and 3,4-methylenedioxymethamphetamine (MDMA) fully substituted for mephedrone (Varner et al., 2013). Furthermore, both methamphetamine and MDMA substituted for the discriminative-stimulus effects of 3,4-methylenedioxypyrovalerone (MDPV; Fantegrossi et al., 2012). Similarly, when the prototypical stimulants amphetamine, methamphetamine, or cocaine were used as the training drug, the synthetic cathinones methcathinone, MDPV, methylone, and mephedrone fully substituted for the training drug (Gatch et al., 2013; Glennon et al., 1995; Schechter, 1997; Young and Glennon, 1993). Studies of intravenous self-administration, where MDPV, methylone, and mephedrone were self-administered in by rodents, have provided evidence that synthetic cathinones also have reinforcing effects (Aarde et al., 2013a; 2013b; Hadlock et al., 2011; Motbey et al., 2013; Watterson et al., 2012; 2013). Taken together, self-

administration and drug discrimination work thus far indicate that certain synthetic cathinones are reinforcers of the stimulant type.

There are relatively little preclinical data characterizing the abuse potential of second-generation synthetic cathinones. A recent study examined methcathinone and four structurally related, second-generation synthetic cathinones, 4-MEC, 3-fluoromethcathinone (3-FMC), pentedrone, and pentylone. All compounds fully substituted for cocaine and methamphetamine (Gatch et al., 2014). Furthermore, the mechanisms of action of the second-generation synthetic cathinones in the current report have been investigated. Both alpha-PVP and 4-MePPP inhibit uptake of dopamine and serotonin, with the greatest effects on dopamine (Marusich et al., 2014; Saha et al., 2014). 4-MEC inhibits reuptake at all monoamine transporters but also functions as a serotonin releaser (Saha et al., 2014; Simmler et al., 2014). In order to expand current knowledge on this emerging drug class, the goal of the present study was to characterize the discriminative-stimulus effects of three, second-generation synthetic cathinones (4-MePPP, 4-MEC, and alpha-PVP) in rats trained to discriminate methamphetamine from saline.

2. Materials and Methods

All animal-use procedures were approved by the University of Mississippi Medical Center's Institutional Animal Care and Use Committee and were in accordance with the National Research Council's Guide for Care and Use of Laboratory Animals (8th edition, 2011).

2.1 Animals and Apparatus

Nine male Sprague-Dawley rats at approximately 70 days of age and weighing between 260 and 300g at the start of the experiment served as subjects. Rats were single-housed and acclimated to the animal facility for approximately one week before behavioral testing. Subjects were maintained at 85% of their free-feeding weights, which increased across the experiment according to a standardized growth curve. Water was available *ad libitum* throughout the experiment. The room was maintained on a 12-h light-dark cycle (lights on at 8:00am).

Sessions took place during the light phase in five, 8.75" × 10" operant chambers (Med-Associates). Each chamber was contained within a sound-attenuating box equipped with a ventilation fan to minimize noise. Two response levers with stimulus lights above them were mounted on the walls of each chamber, and a food receptacle was located between the levers. Each chamber was illuminated with a single houselight, which was located on the wall opposite the levers and food receptacle. A Macintosh computer with custom software and interfaces controlled data collection and session parameters.

2.2 Procedure

Sessions were conducted Sunday through Friday at approximately the same time each day. Rats were trained to lever press for food pellets (45 mg, Bio-Serve, grain-based pellets) on a fixed-ratio (FR) 1 schedule. Once lever pressing was acquired (1-3 sessions), defined as 50 total lever presses in a single session, discrimination training began. For half of the subjects, the left lever was associated with a 1.0 mg/kg methamphetamine injection and the right with

a saline injection, and the reverse condition was true for the other subjects. Injections and discrimination training continued while the FR was simultaneously increased to a terminal FR 20. A reset contingency remained in effect for all sessions so responses on the opposite lever prior to completion of the FR reset the FR for both levers.

Sessions began with a 15-min blackout, during which all lights were darkened, and lever pressing was recorded but had no programmed consequences. At the end of the blackout, stimulus lights above both levers were illuminated and correct responses resulted in delivery of a food pellet. Initial training sessions lasted 30 min, excluding the blackout, and were conducted on a single alternation schedule (SDSD; S, saline; D, drug). Session length was gradually decreased to 15 minutes as training progressed.

Once discrimination was acquired, defined as 80% correct-lever responses prior to the first reinforcer delivery and 90% correct-lever responses for the entire session for seven of eight consecutive sessions, training continued on a double-alternation schedule (i.e., SSDD). Testing began once all terminal conditions were in effect (15-min sessions, FR 20, and double alternation) and subjects met the acquisition criteria described above for correct-lever responses.

Substitution tests were introduced into the double alternation sequence (SDTDSTSDTDST; T, test). Tests occurred if the prior eight training sessions met criteria described above for correct-lever responses. During test sessions, both levers were active, such that 20 consecutive responses on either lever delivered a food pellet. Methamphetamine (0.125-1.0 mg/kg) was tested in all subjects prior to testing other compounds. The order of subsequent compounds tested was counterbalanced across subjects. For the synthetic cathinones, doses were administered in an ascending order in the first one or two subjects tested and were counterbalanced across subjects thereafter. For all other drugs, dose range was selected based on previous research and dose order was counterbalanced across subjects. Each compound was tested in at least eight subjects, and each dose was administered twice, once following saline and once following methamphetamine. Cocaine (1.0-8.0 mg/kg) and pentobarbital (1.0-8.0 mg/kg) were used as positive and negative controls, respectively. The synthetic cathinones, 4-MEC (1.0-8.0 mg/kg), 4-MePPP (4.0-16.0 mg/kg), and alpha-PVP (0.25-2.0 mg/kg), were the experimental compounds tested.

2.3 Data Analysis

Dependent measures (presented as group means) were percent of drug-lever responses before delivery of the first reinforcer and for the entire session. Overall response rates (responses/min) were also calculated and then normalized as percent of control for each dose-effect curve. Control rates were the average response rates taken from saline-training sessions that occurred prior to each test session. Doses of drugs that engendered 80% drug-lever responses were considered to fully substitute for the training dose of methamphetamine, and 20% drug-lever responding was reported as no substitution. To compare relative potencies of drugs that fully substituted for methamphetamine, ED50 values (i.e., the dose that would predict 50% drug-lever responses) were calculated by log-transforming the x-axis and using a best-fitting logistic function (GraphPad Software 6.0).

Drug doses were increased until either full substitution occurred or a statistically significant reduction in response rate for the group was seen relative to saline-control levels.

2.4 Drugs

Final solutions for all drugs were prepared using 0.9% sterile saline. Doses are expressed as the salt form. Cocaine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD, USA). Methamphetamine hydrochloride was purchased from Sigma (St. Louis, MO, USA). Pentobarbital was purchased from the University of Mississippi Medical Center pharmacy (Jackson, MS, USA). The cathinones, 4-MEC, 4-MePPP, and alpha-PVP, were graciously provided by Dr. Bruce Blough at the Research Triangle Institute (Research Triangle Park, NC, USA) and were synthesized as hydrochloride salts. All drugs were injected intraperitoneally in a volume of 1 ml/kg.

3. Results

Acquisition of methamphetamine discrimination took an average of 67 days (95% CI=49-85). Methamphetamine dose-dependently substituted for the training dose (1.0 mg/kg) in all animals, with complete substitution at 1.0 mg/kg. Figure 1 shows mean percent drug-lever responses per session (top panel), mean percent drug-lever responses before delivery of the first reinforcer (middle panel) and mean response rates (responses/min as percent of control; bottom panel) for methamphetamine, cocaine, and pentobarbital (left panels) and the synthetic cathinones (right panels). Cocaine fully substituted for the training dose of methamphetamine, and pentobarbital did not substitute. Alpha-PVP and 4-MePPP fully substituted for the training dose of methamphetamine. For alpha-PVP and 4-MePPP, total drug-lever responses reached 88.6% and 89.0% at 2.0 and 16.0 mg/kg doses, respectively. For percent drug-lever responses prior to the delivery of the first reinforcer, the group mean for the highest dose that substituted for methamphetamine was 93.3% for alpha-PVP and 99.7% for 4-MePPP. Depending on the dependent measure, 4-MEC did not substitute for methamphetamine with 15.9% drug-lever responses per session or partially substituted with 34.5% drug-lever responses before the first reinforcer. Higher doses were not tested because a significant reduction in response rates was observed.

Control response rates (Figure 1, bottom panels) were significantly, and dose-dependently reduced for methamphetamine [$F(3,35)=13.9$, $p<0.001$], alpha-PVP [$F(4,39)=7.8$, $p<0.05$], 4-MePPP [$F(3,31)=10.2$, $p<0.01$], 4-MEC [$F(4,39)=13.1$, $p<0.001$], cocaine [$F(4,44)=9.8$, $p<0.01$], and pentobarbital [$F(4,29)=8.8$, $p<0.05$]. Bonferroni comparisons indicated significant reductions for 1.0 mg/kg methamphetamine, 2.0 mg/kg alpha-PVP, 16.0 mg/kg 4-MePPP, 2.0 and 8.0 mg/kg 4-MEC, 2.0, 4.0, and 8.0 mg/kg cocaine, and 8.0 mg/kg pentobarbital ($p's<0.05$).

The rank order of potency for drugs that fully substituted for methamphetamine was: methamphetamine > alpha-PVP > cocaine > 4-MePPP. Relative to methamphetamine, alpha-PVP (ED₅₀=0.7 mg/kg) was approximately 2.5 times less potent (ED₅₀=0.3 mg/kg), 4-MePPP (ED₅₀=4.8 mg/kg) was approximately 18 times less potent, and cocaine (ED₅₀=3.3 mg/kg) was approximately 12 times less potent.

4. Discussion

To our knowledge, this is the first report to compare discriminative-stimulus effects of 4-MePPP and alpha-PVP to an illicit stimulant and the second report comparing 4-MEC to methamphetamine. The results of the present study demonstrated that alpha-PVP and 4-MePPP produce subjective effects similar to those of methamphetamine and therefore may have similar potential for abuse. However, 4-MEC did not substitute for the discriminative-stimulus effects of methamphetamine at a dose that significantly reduced response rates.

The pharmacological mechanisms that mediate the subjective effects of stimulants are associated with their ability to increase extracellular levels of monoamines (Munzar et al., 1999; Spealman et al., 1995; Walsh and Cunningham, 1997). Methamphetamine releases noradrenaline and dopamine with the greatest potencies, followed by serotonin with much lower potency (Rothman et al., 2001). Existing *in vitro* data for the synthetic cathinones tested in the current study demonstrates that they produce actions at monoamine transporters that are typical of illicit stimulants. Alpha-PVP is a catecholamine reuptake inhibitor (Marusich et al., 2014). Because dopamine plays a primary role in the methamphetamine discriminative stimulus, (Czoty et al., 2004; Desai et al., 2010), the finding that alpha-PVP fully substitutes for methamphetamine is not surprising. 4-MePPP is a dopamine-preferring reuptake inhibitor, with very little activity at the serotonin transporter (Saha et al., 2014). Its potency for the dopamine transporter is low relative to alpha-PVP, and this is consistent with the finding that it also has a lower potency for substitution of methamphetamine's discriminative-stimulus effects. Taken together, our data and recent *in vitro* work (Marusich et al., 2014; Saha et al., 2014) suggest that catecholamine reuptake inhibition mediates the ability of these two compounds to substitute for methamphetamine. Further elucidation of the mechanisms of action of the discriminative-stimulus effects of synthetic cathinones could be done using receptor antagonists for the various monoamine receptors (e.g., see Young and Glennon, 1998).

A recent study by Gatch et al. (2014) found that 4-MEC fully substituted for both 1.0 mg/kg methamphetamine and 10.0 mg/kg cocaine, a finding inconsistent with the current report. Two methodological differences distinguish their study from the current one and could account for the discrepant results. First, the dose of 4-MEC (50.0 mg/kg) that fully substituted for methamphetamine was much larger than the doses tested in the present study (1.0-8.0 mg/kg). Second, the pretreatment for 4-MEC in the prior study was 30 min and in the current study was 15 min. Furthermore, *in vitro* data for 4-MEC show a unique profile of interaction with monoamine transporters relative to other synthetic cathinones. 4-MEC inhibits uptake at all three monoamine transporters (Simmler et al., 2014) but has been identified as a ligand with mixed or 'hybrid' transporter activity (Blough et al., 2014; Saha et al., 2014). 4-MEC induces serotonin release and inhibits reuptake of dopamine and norepinephrine. Temporal differences between these two mechanisms of action may produce variances in 4-MEC's discriminative-stimulus profile. For example, early release of serotonin may occur prior to buildup of dopamine and norepinephrine at the synaptic cleft, which could explain different results obtained with different pretreatment times.

In summary, the results of the present study show that some second-generation synthetic cathinones have subjective effects similar to methamphetamine. Future studies are needed to determine the safety and toxicology profiles of these drugs. Additional tests of abuse potential (e.g., drug self-administration) are also needed to fully determine whether these synthetic cathinones present similar abuse potential to illicit stimulants.

Acknowledgments

We dedicate this report to Dr. William L. Woolverton (b. 1950, d. 2013), our mentor, colleague, and friend. Dr. Woolverton had a great passion not only for studying the behavioral effects of drugs of abuse, but also for training future researchers in this field. His influence and mentorship are missed but are not forgotten.

The authors would also like to gratefully acknowledge Muzamil A. Khawaja for his technical assistance in conducting this research.

Role of Funding Source: The research reported in this manuscript was supported by The UMMC Drug Abuse Development Fund and R01 DA12970 to BEB.

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Highlights

- We tested the discriminative stimulus effects of second-generation synthetic cathinones in methamphetamine-trained rats.
- Alpha-PVP and 4-MePPP both substituted for methamphetamine.
- 4-MEC did not substitute for methamphetamine.

Figure 1.

Discriminative-stimulus effects of drugs tested in rats trained to discriminate 1.0 mg/kg methamphetamine from saline. In each panel, S represents saline test sessions and MA 1.0 represents 1.0 mg/kg methamphetamine test sessions. Left panels represent data for methamphetamine (n=9), cocaine (n=9), and pentobarbital (n=8). Right panels represent data for alpha-PVP (n=8), 4-MePPP (n=8), and 4-MEC (n=8). Each data point represents the group mean. The dotted line at 80% and 20% drug-lever responses represents threshold levels for full and partial substitution, respectively. All points represent the mean of all subjects tested for a particular drug, except at doses when some subjects did not earn any reinforcers. When this occurred, the number of subjects is indicated in parenthesis for that dose. All error bars represent the standard error of the mean (SEM).