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Discriminative and locomotor effects of five synthetic cathinones in rats and mice

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Abstract

Rationale—Synthetic cathinones continue to be sold as “legal” alternatives to methamphetamine or cocaine. As these marginally legal compounds become controlled, suppliers move to other, unregulated compounds.

Objectives—The purpose of these experiments was to determine whether several temporarily controlled cathinone compounds, which are currently abused on the street, stimulate motor activity and have discriminative stimulus effects similar to cocaine and/or methamphetamine.

Methods—Methcathinone, pentedrone, pentylone, 3-fluoromethcathinone (3-FMC), and 4-methylethcathinone (4-MEC) were tested for locomotor stimulant effects in mice and subsequently for substitution in rats trained to discriminate cocaine (10 mg/kg, i.p.) or methamphetamine (1 mg/kg, i.p.) from saline.

Results—Methcathinone, pentedrone, and pentylone produced locomotor stimulant effects which lasted up to 6 hours. In addition, pentylone produced convulsions and lethality at 100 mg/kg. 4-MEC produced locomotor stimulant effects which lasted up to 2 hours. Methcathinone, pentedrone, pentylone, 3-FMC, and 4-MEC each produced discriminative stimulus effects similar to those of cocaine and methamphetamine.

Conclusions—All of the tested compounds produce discriminative stimulus effects similar to either those of cocaine, methamphetamine or both, which suggests that these compounds are likely to have similar abuse liability to cocaine and/or methamphetamine. Pentylone may be more dangerous on the street, as it produced adverse effects at doses that produced maximal stimulant-like effects.

Keywords

cathinones; drug discrimination; locomotor activity; abuse liability; mouse; rat

Introduction

Since the synthetic cathinones marketed as “bath salts” or “legal highs” that have recently emerged (UNODC 2013) have been controlled in the USA and other countries, other

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compounds have replaced them in gray market preparations. Several of the more commonly used compounds are structurally based on methcathinone, which is a well-known congener of cathinone that was widely abused in Europe (Calkins et al. 1995; Emerson and Cisek 1993). Its molecular and behavioral effects have been well characterized. Methcathinone acts at monoamine transporters where it produces release of DA and NET, and less potently, 5-HT (Cozzi et al. 2013; Eshleman et al. 2013; Glennon et al. 1987). It produces discriminative stimulus effects comparable to that of other psychostimulants, fully substituting for amphetamine (Glennon et al. 1987; Schechter 1997b) and cocaine (Kohut et al. 2013; Li et al. 2006; Schechter 1997a). Similarly, methamphetamine, amphetamine, and cocaine substitute in methcathinone-trained rats (Young and Glennon 1998). Further, methcathinone maintains self-administration in baboons (Kaminski and Griffiths 1994) and facilitates ICSS in rats (Bonano et al. 2014).

Four of these synthetic compounds, including 4-methylethcathinone (4-MEC), 3-fluoromethcathinone (3-FMC), pentedrone, and pentylone, have been temporarily scheduled as Schedule I compounds (Drug Enforcement Administration 2014). Use of 3-FMC has been seen in Israel and Germany since 2009 (Meyer et al. 2012). 4-MEC, 3-FMC, pentylone, pentedrone and MDAI have been found in samples of “bath salts” or in blood samples of users increasingly over the past 4 years (Elliott and Evans 2014; Gil et al. 2013; Marinetti and Antonides 2013; Uralets et al. 2014). Further, there is increasing evidence of possible harm of these substances. Hepatoxicity of “legal high” packages with synthetic cathinones including pentedrone and 4-MEC has been reported (Araújo et al. 2014).

Identification of abuse liability is based on several factors, including chemical structures, pharmacological mechanisms, and behavioral effects similar to known drugs of abuse. The present compounds are chemically related to known, controlled substances of abuse such as methamphetamine and methcathinone. A recent study examined the effects of some of these cathinones on monoamine transporters and receptors (Simmler et al. 2014). 4-MEC and pentylone inhibited uptake of DA, NE and 5-HT, whereas 3-FMC inhibited uptake of only NE and DA. 4-MEC and pentylone also caused 5-HT release, whereas 3-FMC produced DA and NE release. In contrast, pentedrone inhibited uptake of NE and DA, but did not produce release of DA, NE or 5-HT. None of these three cathinones showed significant levels of binding to monoamine receptors (Simmler et al., 2014).

Behavioral studies of the abuse liability of potential psychostimulants include locomotor activity, discriminative stimulus effects similar to controlled substances such as cocaine or methamphetamine, conditioned place preference, and finally, the ability to maintain drug seeking behavior in a self-administration test. The behavioral effects of methcathinone have been well characterized. One study reported that 3-FMC increased locomotor activity and decreased performance on the rotarod and produced ataxia in mice (Marusich et al. 2012). Other cathinone compounds, including mephedrone, methylone, butylone, mephedrone, 3,4-methylenedioxypyrovalerone (MDPV), and 4-FMC, have been reported to produce increases in locomotor activity (see review by Glennon, 2014), and fully substitute for the discriminative stimulus effects of cocaine, amphetamine, and methamphetamine (Dal Cason et al., 1997; Gatch et al., 2013). Further, methamphetamine and MDMA fully substituted in MDPV-trained rats (Fantegrossi et al., 2013).

In order to provide evidence regarding potential abuse liability, the current study examines the behavioral effects of methcathinone and four structurally related compounds found on the street, 4-methylethcathinone (4-MEC), 3-fluoromethcathinone (3-FMC), pentedrone, and pentylone. The ability of these compounds to alter locomotor activity in mice was tested, as well as their ability to substitute for the discriminative stimulus effects of cocaine and/or methamphetamine. As mentioned previously, the abuse liability of methcathinone has been well-established. The extent to which the other cathinones produce behavioral effects similar to those of methcathinone (in locomotor activity) and cocaine or methamphetamine (in drug discrimination) will provide support for the hypothesis that the four test compounds have abuse liability comparable to cocaine, methamphetamine and/or methcathinone.

Methods

Subjects

Male Swiss–Webster mice were obtained from Harlan (Indianapolis, IN) at approximately 8 weeks of age and tested at approximately 10 weeks of age. Mice were group housed (3-4 per cage) on a 12:12-h light/dark cycle and were allowed free access to food and water in the home cages. Male Sprague-Dawley rats were obtained from Harlan-Sprague Dawley (Indianapolis, IN). All rats were housed individually and were maintained on a 12:12 light/dark cycle (lights on at 7:00 AM). Body weights were maintained at 320-350 g by limiting food to 20 g/day which included the food received during discrimination training sessions. Water was readily available in the home cages. All housing and procedures were in accordance with Guidelines for the Care and Use of Laboratory Animals (National Research Council 2011) and were approved by the University of North Texas Health Science Center Animal Care and Use Committee.

Locomotor Activity

The study was conducted using 40 Digiscan (model RXYZCM, Omnitech Electronics, Columbus, OH) locomotor activity testing chambers (40.5 × 40.5 × 30.5 cm) housed within sound-attenuating chambers in sets of two. A panel of infrared beams (16 beams) and corresponding photodetectors were located in the horizontal direction along the sides of each activity chamber. A 7.5-W incandescent light above each chamber provided dim illumination and fans provided an 80-dB ambient noise level within the chamber.

Separate groups of 8 mice were injected with either vehicle (0.9% saline) or a test compound: methcathinone, 3-FMC (0.3, 1, 3, 10 or 30 mg/kg); pentylone, 4-MEC (3, 10, 30 or 100 mg/kg); or pentedrone (1, 2.5, 5, 10 or 25 mg/kg), immediately prior to locomotor activity testing. In all studies, horizontal activity (interruption of photocell beams) was measured for 8 hours within 10-min periods, beginning at 0800 hrs (1 hr after lights on). Behavioral observations were recorded on each mouse during the test sessions at 30, 120 and 480 minutes following 25 mg/kg (pentedrone), 30 mg/kg (methcathinone, 3-FMC) or 100 mg/kg (pentylone, 4-MEC).

Discrimination Procedures

Standard behavior-testing chambers (Coulbourn Instruments, Allentown, PA) were connected to IBM-PC compatible computers via LVB interfaces (Med Associates, East Fairfield, VT). The computers were programmed in Med-PC for Windows, version IV (Med Associates, East Fairfield, VT) for the operation of the chambers and collection of data.

Using a two-lever choice methodology, a pool of 34 rats previously trained to discriminate methamphetamine (1 mg/kg) and a pool of 27 rats previously trained to discriminate cocaine (10 mg/kg) from saline were tested as previously described (Gatch et al. 2011). Rats received an injection of either saline or drug and were subsequently placed in the behavior-testing chambers, where food (45 mg food pellets; Bio-Serve, Frenchtown, NJ) was available as a reinforcer for every ten responses on a designated injection-appropriate lever. The pretreatment time was 10 min. Each training session lasted a maximum of 10 min, and the rats could earn up to 20 food pellets. The rats received approximately 60 of these sessions before they were used in tests for substitution of the experimental compounds. Rats were used in testing once they had achieved 9 of 10 sessions at 85% injection-appropriate responding for both the first reinforcer and total session. The training sessions occurred on separate days in a double alternating fashion (drug-drug-saline-saline-drug; etc.) until the training phase was complete, after which substitution tests were introduced into the training schedule such that at least one saline and one drug session occurred between each test (drug-saline-test-saline-drug-test-drug; etc.). The substitution tests occurred only if the rats had achieved 85% injection-appropriate responding on the two prior training sessions.

Test sessions lasted for a maximum of 20 min. In contrast with training sessions, both levers were active, such that 10 consecutive responses on either lever led to reinforcement. Data were collected until the first reinforcer was obtained, or for a maximum of 20 min. Each compound was tested in groups of six rats. A repeated-measures design was used, such that each rat was tested at all doses of a given drug. Pretreatment times were based on peak stimulant activity in the locomotor activity testing. Intraperitoneal injections (1 ml/kg) of saline, methcathinone (0.1 – 1 mg/kg), pentedrone (0.5 – 5 mg/kg), pentylone (1 – 10 mg/kg), or 3-FMC (0.25 – 2.5 mg/kg) occurred 15 min prior to the start of the test session. 4-MEC (1 – 50 mg/kg) was administered 30 min prior to the start of the test session.

Drugs

(-)-Cocaine hydrochloride, (+)-methamphetamine hydrochloride, (d,l)-N-methcathinone hydrochloride, pentedrone hydrochloride (2-(methylamino)-1-phenylpentan-1-one), pentylone hydrochloride (β-keto-methylbenzodioxolyl-pentanamine), 4-MEC hydrochloride (4-methylethcathinone) and 3-FMC hydrochloride (3-fluoromethcathinone) were provided by the National Institute on Drug Abuse Drug Supply Program. All drugs were dissolved in 0.9% saline and were administered i.p. in a volume of 1 ml/kg.

Data Analysis

Locomotor activity data were expressed as the mean number of photocell counts in the horizontal plane (ambulation counts) during each 10-min period of testing. A 30-min period, beginning when maximal stimulation of locomotor activity first appeared as a function of

dose, was used for analysis of dose-response data and calculation of ED50 values. TableCurve 2D was used to estimate the peak ambulation following administration of each cathinone analog. The ED50 values and the standard error of the mean were then calculated by estimating the dose producing ½ of the peak ambulation from the ascending linear portion of the dose response curve. A two-way repeated measures analysis of variance (Treatment × Time Period) was conducted on horizontal activity counts/10 min interval. A one-way ANOVA was conducted on horizontal activity counts for the 30-min period of maximal effect, and planned comparisons were conducted for each dose against saline control using single degree-of-freedom F tests. A one-way ANOVA was conducted on peak ambulation (percent of vehicle control) for the 5 test compounds.

Drug discrimination data are expressed as the mean percentage of drug-appropriate responses occurring in each test period. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Graphs for percent drug-appropriate responding and response rate were plotted as a function of dose of test compound (log scale). Percent drug-appropriate responding was shown only if at least 3 rats completed the first fixed ratio. Full substitution was defined as >80% drug-appropriate responding and not statistically different from the training drug.

The potencies of methcathinone, pentedrone, pentylone, 4-MEC and 3-FMC were calculated by fitting straight lines to the dose-response data for each compound by means of Origin (OriginGraph, Northhampton, MA). Straight lines were fitted to the linear portion of dose-effect curves, including not more than one dose producing <20% of the maximal effect and not more than one dose producing >80% of the maximal effect. Other doses were excluded from the analyses. Differences among ED50 values were tested by one-way ANOVA followed by Tukey's test to compare individual means. Rates of responding were expressed as a function of the number of responses made divided by the total session time. Response rate data was analyzed by one-way repeated measures analysis of variance. Effects of individual doses were compared to the vehicle control value using a priori contrasts. The criterion for significance was set a priori at $p<0.05$.

Results

Locomotor activity

Figure 1 shows average horizontal activity counts/10 min as a function of time (0-8 hr) and dose of each test compound. The two-way analysis of variance performed on data for each compound except 4-MEC yielded a significant main effect of Treatment, as well as a Treatment × Time Period interaction (all *p*s <0.05). Figure 2 shows dose-effect curves generated from the time of peak effect (from shaded area in Fig 1) for each compound. The one-way analysis of variance for maximal effect yielded a significant effect for each compound (all *p*s <0.05). In addition, methcathinone produced a larger peak effect than the other four cathinones [$F(4,115)=3.673$, $p=0.007$]. The peak effects produced by pentedrone, pentylone, 4-MEC and 3-FMC were not different ($p>0.05$).

Treatment with methcathinone resulted in time- and dose-dependent stimulation of locomotor activity in doses from 1 to 30 mg/kg. Stimulant effects of 1 to 10 mg/kg occurred

within 10 minutes following injection and lasted 100 to 180 minutes. Methcathinone depressed locomotor activity between 10 and 60 min following administration of 30 mg/kg. A dose effect curve generated from the time of peak effect shows a dose-dependent increase in locomotor activity (ED_{50}=1.39±0.09 mg/kg) followed by a sharp decrease in locomotor activity, since stimulant effects of 30 mg/kg did not occur until 90 to 270 min after administration. During the period of peak effect (0-30 min), locomotor activity increased to a peak of 267 ± 20% of vehicle control following 10 mg/kg.

Pentedrone produced time- and dose-dependent stimulation of locomotor activity in doses from 2.5 to 25 mg/kg (ED_{50}=4.70±0.10 mg/kg). Stimulant effects of 2.5 to 10 m g/kg occurred within 10 minutes following injection and lasted 90 to 140 minutes (Fig 1). During the period of peak effect (0-30 min), locomotor activity increased to a peak of 196 ± 11% of vehicle control following 10 mg/kg (Fig 2). Treatment with 3-FMC produced time- and dose-dependent stimulation of locomotor activity in doses from 1 to 30 mg/kg (ED_{50}=2.14±0.06 mg/kg). Stimulant effects of 1 to 10 mg/kg occurred within 10 minutes following injection and lasted 40 to 170 minutes. Stimulant effects were delayed following 30 mg/kg. During the period of peak effect (0-30 min), locomotor activity increased to a peak of 204 ± 17% of vehicle control following 10 mg/kg.

Treatment with pentylone resulted in time- and dose-dependent stimulation of locomotor activity in doses from 10 to 100 mg/kg (ED_{50}=11.54±0.08 mg/kg). Stimulant effects of 10 and 30 mg/kg occurred within 10 minutes following injection and lasted 120 to 170 minutes (Fig 1). Stimulant effects of 100 mg/kg did not occur until 2 to 6 h after administration. During the period of peak effect (0-30 min), locomotor activity increased to a peak of 207 ± 16% of vehicle control following 10 mg/kg (Fig 2). Lethality occurred in 1/8 mice within the 30-40 min time bin following 100 mg/kg pentylone. Clonic convulsions were observed in 3/7 mice at 8 h following 100 mg/kg pentylone. 4-MEC produced time- and dose-dependent stimulation of locomotor activity in doses from 30 to 100 mg/kg (ED_{50}=21.09±0.09 mg/kg). Stimulant effects occurred within 30 minutes following injection and lasted 110 minutes. During the period of peak effect (30-60 min), locomotor activity increased to a peak of 190 ± 12% of vehicle control following 10 mg/kg.

Discrimination

Methcathinone, pentedrone, pentylone, 3-FMC and 4-MEC fully substituted for the discriminative stimulus effects of methamphetamine and cocaine (Figures 3 and 4). ED50 values are shown in Table 1. There were no differences in the potency of the test compounds in cocaine- and methamphetamine-trained rats ($p>0.05$). Pentylone decreased rate of responding in methamphetamine-trained rats [$F(4,20)=4.87$, $p=.007$], whereas 4-MEC decreased rate of responding in cocaine-trained rats [$F(4,20)=4.81$, $p=.007$]. The other cathinone compounds produced no effect on rate of responding.

Discussion

Ten compounds were recently temporarily placed into Schedule I, including 4-MEC, 4-MePPP, α-PVP, butylone, pentedrone, pentylone, 4-FMC, 3-FMC, naphyrone, and α-PBP (Drug Enforcement Administration 2014). Behavioral data on three of these compounds

(butylone, 4-FMC and naphyrone) have been published previously (Gatch et al. 2013; López-Arnau et al. 2012). In the present study, methcathinone, pentedrone, pentylone, 4-MEC and 3-FMC stimulated locomotor activity, producing a range of effects from 2.5 to 6 h duration. These findings agree with earlier studies that methcathinone and 3-FMC stimulate motor activity (van der Schoot et al., 1962; Glennon et al., 1987; Marusich et al., 2012). In fact, several cathinone compounds, including mephedrone, methylone, butylone, mephedrone, MDPV, and 4-FMC, have been reported to produce increases in locomotor activity by several laboratories, which is not surprising as they all act at monoamine transporters like classic psychostimulants such as cocaine and amphetamines (see review by Glennon, 2014).

All of the compounds but 4-MEC produced inverted U-shaped dose effect curves similar to that of methcathinone, a well-characterized compound of abuse. Methcathinone was the most efficacious compound, producing the biggest peak effect relative to control. The peak effects produced by the other compound were not statistically different from each other. The stimulant effects of 4-MEC had a slower onset than for the other compounds (30-60 min vs. 0-30 min). The decrease in locomotor activity seen in the other compounds did occur at the highest dose of 4-MEC (100 mg/kg), but occurred at a time range earlier than that of the peak stimulant effects, and therefore was not seen in the dose-effect curve. Delayed effects were seen following large doses of methcathinone, 3-FMC and pentylone, similar to those reported previously for methamphetamine, MDPV, and naphyrone (Gatch et al., 2013). This effect is seen most strongly in those compounds that produce sharply biphasic dose-effect curves, and may be observed when metabolism of the test compounds reduces concentrations to levels that are associated with larger behavioral effects.

All of the test compounds fully substituted for the discriminative stimulus effects of cocaine, although substantial rate depression was seen for 4-MEC. Similarly, all of the test compounds fully substituted for the discriminative stimulus effects of methamphetamine in the present study. All of the compounds had comparable potencies when tested in methamphetamine- or in cocaine-trained rats. Despite the physiological differences between the species, mouse locomotor activity data have been excellent at predicting dose ranges and pretreatment times for cocaine and methamphetamine drug discrimination in rats in the present study, as well as in prior studies (Carroll et al., 2009; Katz et al., 2001; Gatch et al., 2013).

Methcathinone has been shown to fully substitute in both methamphetamine- and cocaine-trained subjects (Bondareva et al. 2002; Kohut et al. 2013; Schechter 1997a), and cocaine fully substitutes in S(−)-methcathinone-trained rats (Young and Glennon 1998). However, there have been no previous reports on the discriminative stimulus effects of pentedrone, pentylone, 4-MEC, or 3-FMC. Given these four compounds have similar chemical structures as methamphetamine and methcathinone, and inhibit the uptake of dopamine and other monoamines similar to abused psychostimulants such as cocaine (Simmler et al. 2014), it is not surprising that these compounds shared discriminative stimulus effects with psychostimulants such as methamphetamine and cocaine. These findings are in agreement with earlier findings that several abused cathinones fully substituted for the discriminative stimulus effects of cocaine, amphetamine and methamphetamine (Dal Cason et al., 1997;

Gatch et al., 2013) and that methamphetamine and MDMA fully substitute in rats trained to discriminate MDPV (Fantegrossi et al., 2013). These compounds do not produce identical effects, as only MDMA fully substituted in mephedrone-trained rats (Varner et al., 2013). In that study, methamphetamine and cocaine produced significant, but sub-maximal amounts of mephedrone-appropriate responding, as did fenfluramine, which suggests that mephedrone may be a more serotonergic compound than many of the other cathinones.

Given that these compounds have similar chemical structures and similar molecular mechanisms of action as known drugs of abuse, produce psychostimulant effects, and produce discriminative stimulus effects similar to those of cocaine and methamphetamine, it is likely that these compounds share the abuse liability of cocaine, methamphetamine, and methcathinone. Only pentylone produced adverse effects in the present experiments; no adverse effects were observed following the other test compounds at the doses tested. Pentylone produced convulsions and lethality at 100 mg/kg in mice. Adverse effects of pentylone were not observed in rats, but only 10 mg/kg was needed to produce full substitution. Whether or not pentylone will produce toxic effects in humans remains to be seen. Confirmation of the abuse liability of these compounds will require study of their reward effects (e.g., conditioned place preference) and their ability to maintain self-administration.

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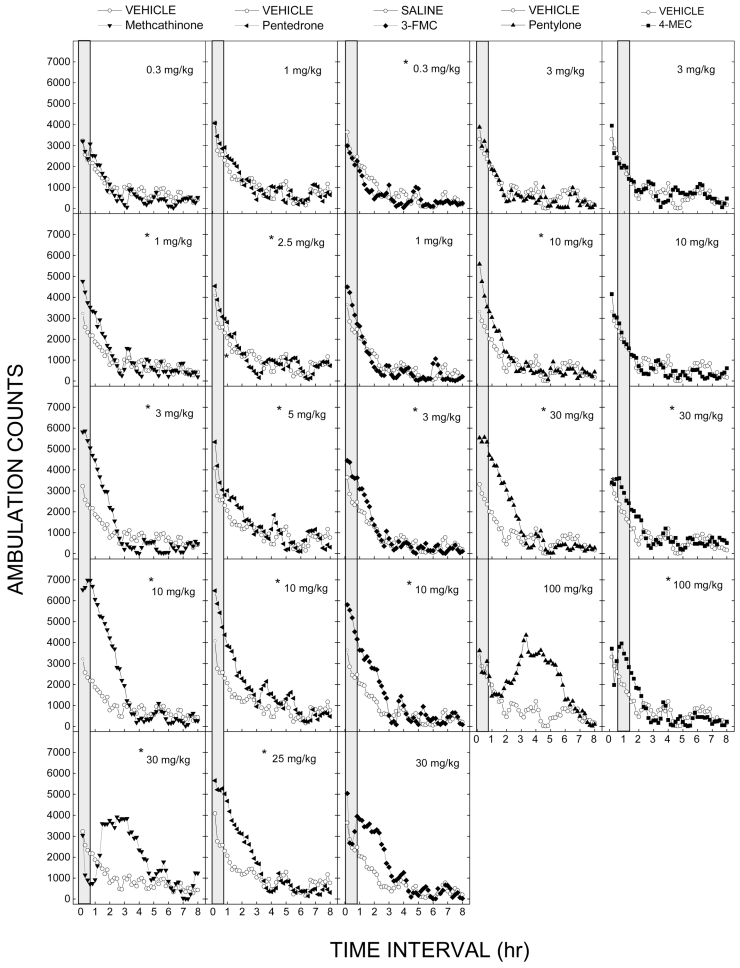

Figure 1. Time course of locomotor stimulant effects

Average horizontal activity counts/10 min (Ambulation counts) as a function of time and dose for methcathinone, pentedrone, 3-FMC, pentylone and 4-MEC. Each panel shows the effects of one dose of compound versus the vehicle. n=8 for each dose. The gray bar shows the time range of peak effect. * indicates stimulant effects ($p < 0.05$) against vehicle control.

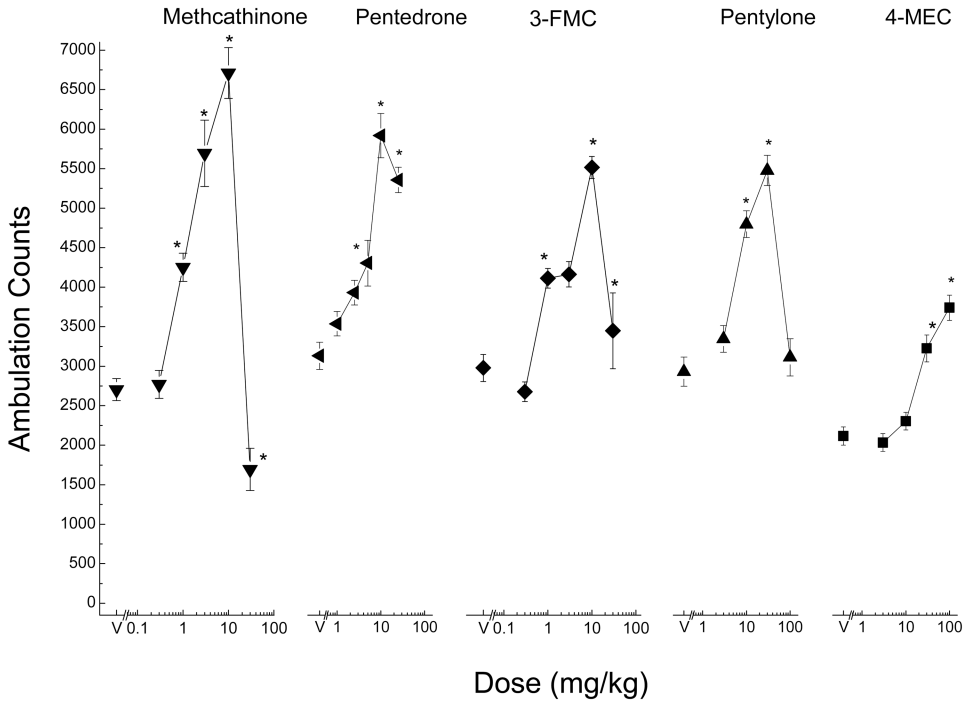

Figure 2. Dose effect of locomotor activity

Average horizontal activity counts/10 min (± SE) during the 30 min of peak effect as a function of dose for each of the five cathinones. All of the cathinones increased ambulation. Methcathinone, pentylone and 3-FMC showed an inverted U-shaped dose response with the highest dose producing ambulation counts less than or equal to vehicle control. n=8 for each dose. V indicates vehicle control. * indicates ($p < 0.05$) against vehicle control.

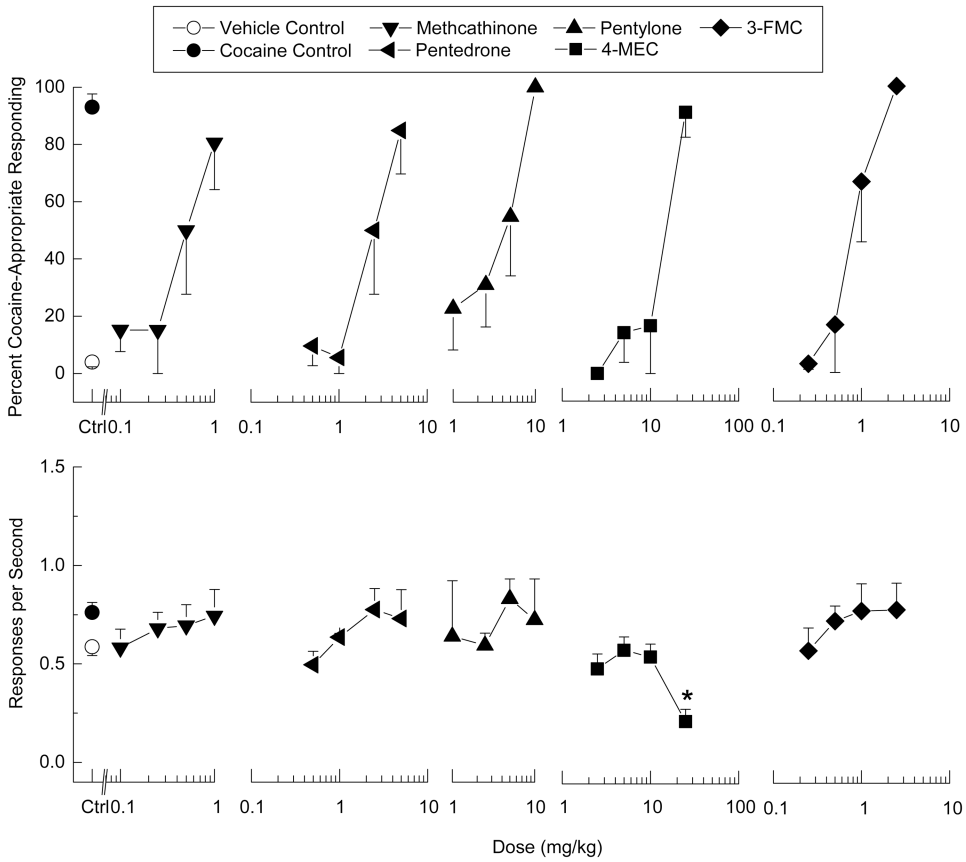

Figure 3. Substitution for the discriminative stimulus effects of cocaine

Top, Percentage of total responses made on the drug-appropriate lever. Bottom, Rate of responding in responses per second (r/s). All of the cathinones fully substituted for the discriminative stimulus effects of cocaine (>80% drug-appropriate responding). n=6 for each compound.

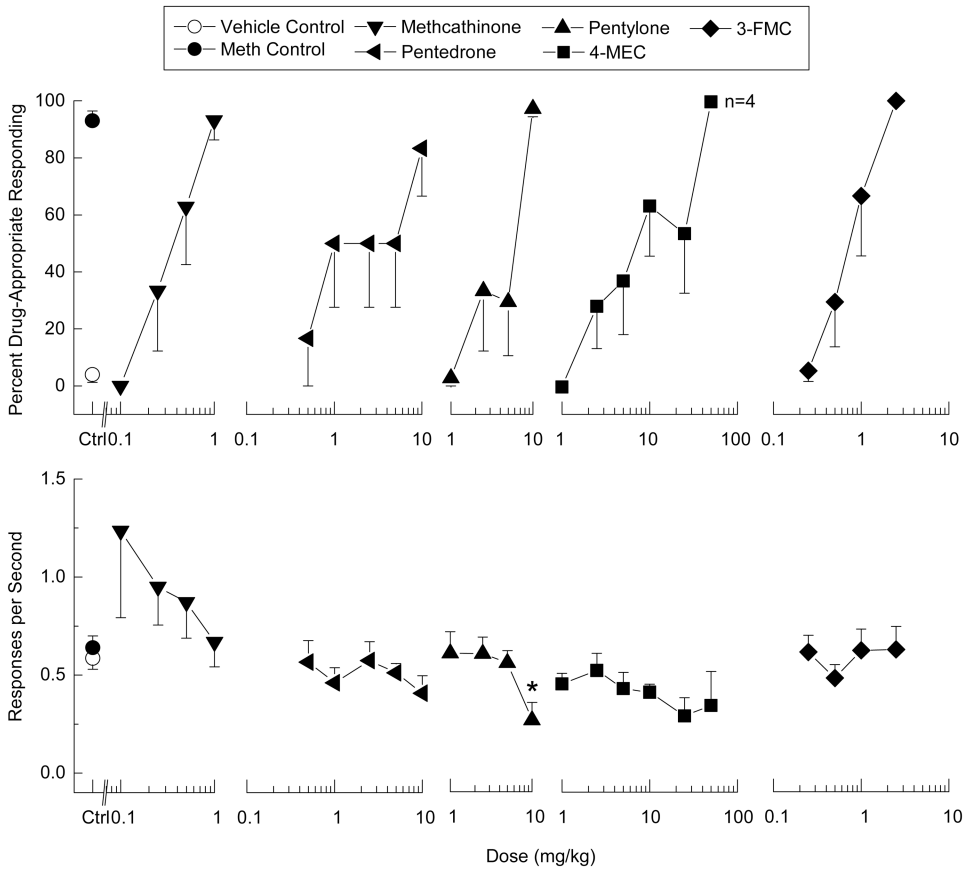

Figure 4. Substitution for the discriminative stimulus effects of methamphetamine

Top: Percentage of total responses made on the drug-appropriate lever. Bottom: Rate of responding in responses per second (r/s). All of the cathinones fully substituted for the discriminative stimulus effects of methamphetamine (>80% drug-appropriate responding). n=6 for each compound except where noted.

Table 1

ED50 values (mg/kg) for discriminative stimulus effects of cathinones in cocaine- and methamphetamine-trained rats. Data shown are the mean ± standard error of the mean. N=6 rats.

Compound	Locomotor Activity	Methamphetamine	Cocaine	Potency Ratio Cocaine/Methamphetamine
Methcathinone	1.39±0.09	0.36±0.08	0.52±0.10	1.44
Pentedrone	4.70±0.10	2.58±0.08	2.29±0.22	1.03
Pentylone	11.54±0.08	4.32±0.09	3.14±0.10	0.73
3-FMC	2.14±0.06	0.74±0.07	0.81±0.07	1.09
4-MEC	21.09±0.09	8.69±0.13	12.54±0.07	1.44