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Behavioral pharmacology of designer cathinones: a review of the preclinical literature

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Abstract

"Bath salts" is one street name for a family of synthetic cathinones that display pharmacological effects resembling cocaine and commonly abused amphetamines. Despite extensive legislation aimed at the criminalization of bath salts, several designer cathinones are gaining a foothold in the illicit drug scene; for example, in the United Kingdom, mephedrone (4-methylmethcathinone, MEPH) is highly popular among drug abusers whereas, in the United States, MDPV (methylenedioxypyrovalerone) and methylone are highly prevalent. To date, knowledge about the hazards of designer cathinones is based mostly on hospital reports and anecdotal evidence derived from online surveys. Despite the paucity of preclinical studies directed toward designer cathinones, a number of invaluable findings arising from those studies are enabling scientists to develop their neuropharmacological profiles. Despite their commonalities in chemical structures, synthetic cathinones possess distinct neuropharmacological profiles and produce different behavioral effects, including unique effects on locomotor activity, learning, anxiety, thermoregulation, and abuse liability. The present review will discuss the behavioral effects of MEPH, MDPV, and methylone and compare those effects to established psychostimulant drugs. The rise in the use of designer cathinones in the United States and abroad justifies further investigations into these compounds, both for a greater understanding of the danger that "bath salts" pose to the public, and to provide insight into replacement cathinones as they emerge onto the market.

Keywords

bath salts; mephedrone; MDPV; methylone; locomotor; psychostimulant; cathinone; amphetamine; pyrovalerone

Introduction

New classes of designer synthetic drugs synthesized to mimic the effects of established drugs of abuse have seen a substantial increase in abuse since 2010, with a twenty-fold

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increase in reported human exposures from 2010 to 2011 (Poison Control Centers, 2011, Deluca et al., 2009, James et al., 2011). Among these new classes of drugs are the synthetic cathinones, a group of β-ketone amphetamine compounds derived from cathinone, the active stimulant in the khat plant (*Catha edulis)* (Carroll et al., 2012). Chemical alterations, and functional group substitutions, to the core structure of the parent cathinone compound have yielded a large number of new synthetic cathinone psychostimulants, the most commonly abused being mephedrone (4-methylmethcathinone, MEPH) in the United Kingdom and MDPV (3,4-methylenedioxypyrovalerone), and methylone (3,4-methylenedioxy-N-methylcathinone) in the United States. In an attempt to circumvent legal repercussions, manufacturers of these synthetic cathinones use slang terms such as “bath salts” and “plant food”. In user reports, “bath salts” are described as having similar psychostimulant effects to those found with cocaine, MDMA, and methamphetamine. This observation has been used by illicit drug manufacturers to dilute the quality of MDMA with synthetic cathinones (Brandt et al., 2010, Brunt et al., 2011, Deluca et al., 2009, Schifano et al., 2011). As “bath salt” use began to rise, the numbers of adverse drug reactions reported to the American Association of Poison Control Centers, and hospitals and clinics, also increased (Poison Control Centers, 2011, 2012, Wilmott, 2013, Wood, 2013). These negative clinical presentations led the United States government to categorize MEPH, MDPV and methylone as Schedule I drugs in October 2011, eventually leading to a permanent Schedule I distinction for MEPH and MDPV in July 2012, and methylone in 2013. Since scheduling of MEPH, MDPV, and methylone, a significant decrease in reported human exposures to the American Association of Poison Control Centers has been observed, including 2,676 reports in 2012 and 690 reports through August 31, 2013 (Poison Control Centers, 2013).

Several studies have been conducted to investigate the mechanism of action of MEPH, MDPV and methylone both in vitro and in vivo. MEPH and methylone act as nonspecific monoamine transporter substrates to increase the release of monoamines through a mechanism resembling amphetamine and MDMA. In contrast, MDPV, through a mechanism that is similar to cocaine, acts as a potent inhibitor of monoamine uptake at the dopamine transporter (DAT), serotonin (5-HT) transporter (SERT), and norepinephrine transporter (NET) (Baumann et al., 2012, Baumann et al., 2013, Eshleman et al., 2013, López-Arnau et al., 2012). A growing number of studies have also investigated behavioral effects of “bath salts” in laboratory animals. This review will focus on the behavioral effects of MEPH, MDPV and methylone as they are currently understood in the literature, specifically highlighting impacts on locomotor activity, learning and memory, thermoregulation, abuse liability. Additionally, when applicable, comparisons of behavioral effects of “bath salts” will be compared to effects of established psychostimulant drugs.

Locomotor Activity

Increases in locomotor activity following administration of MEPH, MDPV, or methylone have been studied across multiple paradigms. MEPH is a weaker psychomotor stimulant compared to the parent compound cathinone, that produces dose-dependent increases in locomotor activity in rats that are relatively rapid in onset and short in duration (Angoa-Pérez et al., 2012, Lisek et al., 2012, Motbey et al., 2012a, Shortall et al., 2012) and mice (López-Arnau et al., 2012, Martínez-Clemente et al., 2012, Marusich et al., 2012). Differences between rat strains are observed, as hyperlocomotion following MEPH administration is greater in Sprague-Dawley rats than in Wistar rats (Wright et al., 2012b). Increased locomotor activity with MEPH is attributed to an increase in extracellular dopamine and 5-HT in the ventral striatum (Kehr et al., 2011). The hyperlocomotion induced by MEPH is attenuated by the dopamine D_1 receptor antagonist SCH 23390 and the 5-HT_{2A} receptor antagonist ketanserin (Lisek et al., 2012, López-Arnau et al., 2012, Martínez-Clemente et al., 2012). Conversely, hyperlocomotion produced by MEPH is

enhanced by the dopamine D_2 receptor antagonist sulpiride, as well as by increases in ambient temperature (Miller et al., 2013). Monophasic increases in total wheel rotations in voluntary exercise wheel-running, similar to those observed with MDMA, are also observed following MEPH administration to rats (Huang et al., 2012). Repeated, intermittent administration of a low dose (0.5 mg/kg) of MEPH produces sensitization of ambulation (Lisek et al., 2012). Paradigms evaluating behavioral sensitization at higher doses (15-30 mg/kg) of MEPH have shown preferential sensitization of repetitive, or stereotyped movements (Gregg et al., 2013). Specifically, in rats treated with repeated MEPH, withdrawn from MEPH, and then challenged with MEPH, sensitization of stereotyped movements is observed using constant- and variable-dosing schedules, using context-dependent and –independent paradigms, and after short (2 days) and longer (10 days) pre-challenge withdrawal intervals. Sensitization of stereotyped movements was also observed following 7 days of repeated MEPH exposure (Gregg et al., 2013, Shortall et al., 2012). In adolescent rats that were administered 10 days of MEPH at 30 mg/kg, no sensitization was detected between days 1 and 10 of repeated exposure; however, in this experiment, only total distance traveled was measured (Motbey et al., 2012b).

Compared to MEPH and methylone, MDPV is more potent in increasing locomotor activity. MDPV increases locomotion in both rats and mice (Fantegrossi et al., 2013, Gatch et al., 2013). MDPV produces a 10-fold increase in observed total distance traveled and stereotypic movements over 1 hour following MDPV exposure compared to cocaine, and shows a longer period of increased ambulation compared to both cocaine and methamphetamine (Aarde et al., 2013b, Baumann et al., 2013, Gatch et al., 2013). MDPV increases wheel activity; however unlike MEPH, the effects were biphasic with lower doses producing higher wheel activity total rotation counts, and vice versa (Huang et al., 2012). Increased stereotypy was also observed with higher doses (1.5 mg/kg) of MDPV, with the magnitude and duration of the said stereotypy being dose dependent (Aarde et al., 2013b, Fantegrossi et al., 2013). Compared to MDPV and MEPH, methylone is less potent in producing hyperlocomotion but does produce dose-dependent increases in locomotor activity in both rats and mice, with a hyperlocomotion effect detected at doses lower than those required for cocaine and methamphetamine (Gatch et al., 2013, López-Arnau et al., 2012, Martínez-Clemente et al., 2012, Marusich et al., 2012).

An important comparison of MEPH, MDPV, and methylone on producing psychostimulant-associated behaviors in mice was conducted by Marusich and colleagues (2012) in which male ICR mice (wild-type, no genetic manipulation) underwent a functional observation battery after acute exposure to each drug. MEPH, MDPV and methylone all produced hyperactivity, head weaving, head circling and stimulation (eg. tense body, sudden darting) at a range of different doses. MDPV was the most potent of the synthetic cathinones, with its responses being similar to that of methamphetamine. Additionally, MDPV and methylone also produced increases in circling, while only MDPV produced increases in stereotyped movements and exploration (eg. reorienting the head and sniffing). A rotorod apparatus was used to determine coordination following MEPH, MDPV, or methylone administration, with only methylone at high doses producing significant decreases in time spent on the rotorod. Taken together, these results indicate unique behavioral profiles for MEPH, MDPV and methylone with both similarities and differences to established drugs of abuse.

Learning and memory and anxiety

Like other psychostimulants, synthetic cathinones affect learning and memory, with each cathinone derivative displaying its own unique profile. Binge MEPH administration (30 mg/kg administered twice daily for 4 days), followed by several weeks of drug abstinence, reduces working memory in T-maze experiments; in contrast, methylone exposure under the same experimental paradigm produces no changes in learning and memory (den Hollander

et al., 2013). In addition, den Hollander and colleagues did not detect any differences in spatial memory, anxiety as measured by the elevated plus maze, and depressive behaviors at different stages of MEPH or methylone abstinence. Repeated exposure to high doses of MEPH (30 mg/kg injected once daily for 10 days), followed by 5 weeks of drug abstinence, produces impairment of novel object recognition in adolescent rats (Motbey et al., 2012b). In rhesus macaques, a single dose of 0.32 mg/kg MEPH improves visuospatial associative memory and learning but produces no significant effects on spatial working memory (Wright et al., 2012b). To date, the effects of MDPV on learning and memory or anxiety have not been reported. However, clinical reports that MDPV produces anxiety, paranoia, memory loss and aggression (Kesha et al., 2013, Murray et al., 2012, Ross et al., 2012) in humans suggests possible impacts on those endpoints.

Thermoregulation

A common adverse effect of synthetic cathinones is a change in body temperature, and the direction of the change is dependent on the frequency of exposure. Acute exposure to MEPH produces hypothermia in rats (Miller et al., 2013, Shortall et al., 2012), and the hypothermic response is potentiated by alpha$_1$ adrenoreceptor and dopamine D_1 receptor blockade. On the other hand, when MEPH is administered repeatedly in a binge paradigm, it produces hyperthermia in both rats and mice (Angoa-Pérez et al., 2012, Baumann et al., 2012), and the MEPH-induced hyperthermia is not enhanced by concomitant administration of methamphetamine (Angoa-Pérez et al., 2013). For acute MEPH administration, the hypothermic response at ambient and elevated temperatures is rat-strain specific, with the reduction in body temperature detected in Wistar but not Sprague-Dawley rats (Wright et al., 2012a). The thermoregulatory profile of acute MEPH is not entirely the same as that of cocaine, which produces hypothermia after acute administration at ambient temperatures but hyperthermia at elevated ambient temperatures (Lomax and Daniel, 1990). MEPH also differs from MDMA and methamphetamine in its thermoregulatory effects. MDMA and methamphetamine produce hyperthermia following acute and repeated exposure at ambient temperature and elevated ambient temperature (Cappon et al., 1997, Dafters, 1994, 1995, Makisumi et al., 1998, Metzger et al., 2000, Paulson and Robinson, 1995, Yoshida et al., 1993). Taken together, MEPH produces hypothermia following acute exposure, while producing hyperthermia following binge models of dosing.

Compared to MEPH, MDPV and methylone exhibit a few important differences in altering body temperature. Acute exposure to MDPV produces hyperthermia at elevated temperatures (28°C) but not at normal ambient temperatures (20-23°C), which contrasts with what is observed for MDMA and methamphetamine (Aarde et al., 2013b, Fantegrossi et al., 2013). Similar to MEPH, methylone produces hyperthermia following binge dosing (3 and 10 mg/kg administered 3 separate times). No investigations into effects of a single dose of methylone on body temperature have been conducted. Further investigations are necessary to determine if methylone exhibits a MEPH-like profile, with hypothermia following acute exposure and hyperthermia after multiple doses.

Abuse Liability

Following user reports indicating that synthetic cathinones are addictive (Winstock et al., 2011), animal models have now been employed to determine if this class of drugs are abuse liable. MEPH produces conditioned place preference (CPP) across different species, specifically rats, mice and invertebrates (planarians) (Lisek et al., 2012, Ramoz et al., 2012) and lowers intracranial self-stimulation thresholds in mice (Robinson et al., 2012). MEPH has also been evaluated in rat self-administration models. Acquisition of MEPH under a fixed-ratio (FR-1) schedule of reinforcement is observed in both nose-poke and lever-pressing paradigms with previous food training, as well as long (4 hours) and short (2 hours)

access intervals (Aarde et al., 2013a, Hadlock et al., 2011, Motbey et al., 2013). Under a progressive ratio schedule of reinforcement that measures the reinforcing strength of MEPH, peak break points are observed at 1 mg/kg/infusion (versus 0.3 mg/kg/infusion methamphetamine). Moreover, self-administration was observed at higher ambient temperatures (27°C) (Hadlock et al., 2011), and in multiple rat strains, with Wistar rats showing higher responses for MEPH than Sprague Dawley rats (Aarde et al., 2013a). Drug discrimination assays have been used to investigate the mechanism of MEPH and to identify commonalities and similarities of that mechanism with established drugs of abuse. MEPH fully substitutes for the discriminative stimulus effects of cocaine (Gatch et al., 2013), and cocaine partially substitutes for the discriminative stimulus effects of MEPH (Varner et al., 2013).

MDPV and methylone have also been investigated for their abuse liability across multiple assays. MDPV lowers intracranial self-stimulation thresholds in rats and is self-administered across multiple doses by Wistar and Sprague-Dawley rats (Aarde et al., 2013b, Watterson et al., 2012b). Higher doses of MDPV produce the highest breakpoints in a progressive-ratio model of reinforcement, and dose-substitution studies indicate that MDPV possesses greater potency and efficacy than methamphetamine. Escalation studies also reveal that MDPV increases drug intake at doses similar to what is observed with methamphetamine (Watterson et al., 2012b). In mice, MDPV discriminates from saline and fully substitutes for MDMA and methamphetamine (Fantegrossi et al., 2013). Methylone is also self-administered across multiple doses under fixed- and progressive-ratio schedules, with higher doses of methylone producing higher breakpoints greater than those observed with MDMA (Watterson et al., 2012a). Unlike MDPV, methylone does not produce dose escalation, but does facilitate intracranial self-stimulation in rats similar to MDPV (Bonano et al., 2013). Discrimination studies do show that methylone fully substitutes for MDMA (Dal Cason et al., 1997), but investigations into whether or not methylone substitutes for other psychostimulant drugs have not been conducted.

Conclusions

Abuse of synthetic cathinones is now commonplace and is even growing to include replacement cathinones. Although designer cathinones share the β-ketone functional group, they still exhibit important differences in their respective behavioral profiles that may ultimately translate into diverse pharmacological effects in drug users. MEPH and MDPV exhibit a profile that is more typical of methamphetamine and cocaine, respectively, while methylone a profile that more closely resembles MDMA. While results from animal behavioral models reviewed here support reports from actual drug users that designer cathinones are addictive, the novelty, diversity, and quantity of the said class of drugs, along with the still limited amount of experimental data about their effects, is an existing barrier to better understanding how their neuropharmacological and addictive profiles compare to established psychostimulants and other commonly abused drugs. Further investigations into the pharmacodynamic and pharmacokinetic properties of designer cathinones, as well as drug-drug interaction studies to determine if combinations of substituted cathinones produce additive, synergistic or sub-additive effects, are needed to better understand the pharmacological impacts of these drugs and develop therapeutic strategies to counter their abuse liability and toxicity.

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