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Minireview

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.

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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 increase in reported human exposures from 2010 to 2011 (Centers AAoPC, 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

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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 (Centers AAoPC, 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 2676 reports in 2012 and 690 reports through August 31, 2013 (Centers AAoPC, 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, 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, and 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., 2013) 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., in press). 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., in press; Shortall et al., 2013). 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 h 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 et al. (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 (e.g. 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 (e.g. reorienting the head and sniffing). A rotarod 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 rotarod. 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