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Perspectives

Psychoactive "bath salts": Not so soothing

Q1 Michael H. Baumann *, John S. Partilla, Kurt R. Lehner

Medicinal Chemistry Section, Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health, 333 Cassell Drive, Suite 4500, Baltimore, MD 21224, USA

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ABSTRACT

Recently there has been a dramatic rise in the abuse of so-called "bath salts" products that are purchased as legal alternatives to illicit drugs like cocaine and 3,4-methylenedioxymethamphetamine (MDMA). Baths salts contain one or more synthetic derivatives of the naturally-occurring stimulant cathinone. Low doses of bath salts produce euphoria and increase alertness, but high doses or chronic use can cause serious adverse effects such as hallucinations, delirium, hyperthermia and tachycardia. Owing to the risks posed by bath salts, the governments of many countries have made certain cathinones illegal, namely: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV). Similar to other psychomotor stimulants, synthetic cathinones target plasma membrane transporters for dopamine (i.e., DAT), norepinephrine (i.e., NET) and serotonin (i.e, SERT). Mephedrone and methylone act as non-selective transporter substrates, thereby stimulating non-exocytotic release of dopamine, norepinephrine and serotonin. By contrast, MDPV acts as a potent blocker at DAT and NET, with little effect at SERT. Administration of mephedrone or methylone to rats increases extracellular concentrations of dopamine and serotonin in the brain, analogous to the effects of MDMA. Not surprisingly, synthetic cathinones elicit locomotor activation in rodents. Stimulation of dopamine transmission by synthetic cathinones predicts a high potential for addiction and may underlie clinical adverse effects. As popular synthetic cathinones are rendered illegal, new replacement cathinones are appearing in the marketplace. More research on the pharmacology and toxicology of abused cathinones is needed to inform public health policy and develop strategies for treating medical consequence of bath salts abuse.

1. "Bath salts" products contain synthetic cathinones

In the past few years, there has been an alarming increase in the abuse of so-called "bath salts" products sold on the internet and in retail shops. These products have no legitimate use as bath additives. Instead, they are purchased as "legal highs" that mimic the effects of illicit drugs like cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) (Coppola and Mondola, 2012; Prosser and Nelson, 2012). Bath salts are given evocative names – "Ivory Wave", "Bliss", "White Lightning" – to entice consumers, and they are labeled "not for human consumption" as a ploy to circumvent laws governing the sale of psychoactive substances (Shanks et al., 2012; Spiller et al., 2011). Baths salts powders are usually self-administered by insufflation, but oral and intravenous (i.v.) routes are also used. Clinical reports indicate that recreational doses of bath salts enhance mood and increase alertness, whereas higher doses or repeated use can lead to dangerous neurological and cardiovascular complications requiring emergency medical care (Borek and Holstege, 2012; Kyle et al., 2011; Ross et al., 2011; Spiller et al., 2011). Data from poison control centers in the US reveal a dramatic spike in the reports of bath salts overdose since 2010 (Centers for Disease Control and Prevention (CDC), 2011; Spiller et al., 2011).

The psychoactive compounds in bath salts powders have been identified as synthetic derivatives of cathinone, a structural analog of amphetamine found in the khat plant (Shanks et al., 2012; Spiller et al., 2011). While the recent rise in synthetic cathinone use is unprecedented, the stimulant properties of khat have been known for centuries (Kalix, 1992), and non-medical use of the synthetic cathinone analog, methcathinone, was prevalent in Russia and Eastern Europe during the 1990s (Rosenbaum et al., 2012). Fig. 1 illustrates the chemical structures of cathinone, methcathinone and 3 popular bath salts constituents: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV). Note that all bath salts compounds share a β-ketophenethylamine moiety as part of their chemical structure; MDPV is unique among the compounds due to the presence of a nitrogen-containing pyrrolidine ring. Some bath salts products consist of single cathinones while others contain a mixture of compounds. MDPV is the chief substance detected in blood and urine from patients hospitalized for bath salts overdose in the US (Spiller et al., 2011), while mephedrone is more commonly associated with adverse clinical outcomes in Europe

* Corresponding author. Tel.: +1 443 740 2660.
E-mail address: mbaumann@mail.nih.gov (M.H. Baumann).

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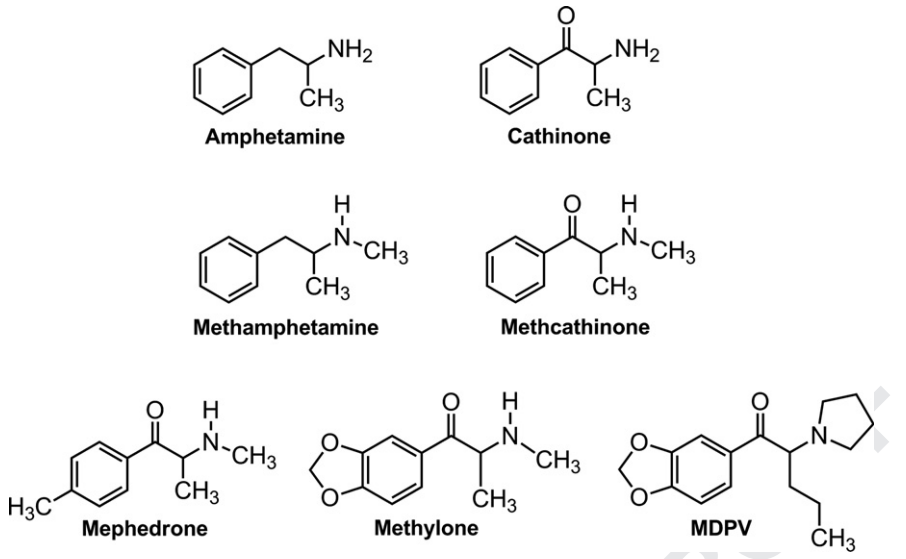

Fig. 1. Chemical structures of cathinone, methcathinone and synthetic bath salts cathinones.

(James et al., 2011). Owing to public health risk posed by bath salts, the governments of many countries have passed laws to render mephedrone, methylone and MDPV illegal (Drug Enforcement Administration (DEA), 2011; Schifano et al., 2011). Unfortunately, a new wave of cathinone derivatives has appeared in the marketplace to replace those drugs now subject to regulatory control (Brandt et al., 2010; Shanks et al., 2012), and the introduction of "replacement" cathinones is expected to continue.

2. Bath salts cathinones target monoamine transporters

Despite the widespread use of bath salts, there is limited information about the mechanism of action underlying the physiological and behavioral effects produced by most synthetic cathinone derivatives. Emerging evidence indicates that bath salts cathinones interact with plasma membrane transporters for dopamine (i.e., DAT), norepinephrine (i.e., NET) and serotonin (i.e., SERT) (Baumann et al., 2012; Cozzi et al., 1999; Hadlock et al., 2011; Lopez-Arnau et al., 2012; Martinez-Clemente et al., 2012; Nagai et al., 2007; Simmler et al., in press; Sogawa et al., 2011). This is not surprising given that cathinone and methcathinone are known substrates (i.e., releasers) at monoamine transporters (Glennon et al., 1987; Kalix, 1992; Rothman and Baumann, 2003; Rothman et al., 2003). On the other hand, there is disagreement in the literature regarding the precise nature of drug-transporter interactions for specific cathinone compounds. Drugs that target monoamine transporters can be classified generally as either substrates (i.e., like amphetamine) or blockers (i.e., like cocaine), and this mechanistic distinction is important to consider for at least two reasons: (1) substrates, but not blockers, are translocated into cells where they disrupt vesicular storage and stimulate non-exocytotic release of neurotransmitters by reversing the normal direction of transporter flux (Rothman and Baumann, 2003; Sitte and Freissmuth, 2010), and (2) substrates can produce persistent deficits in monoamine neurons, including depletion of neurotransmitters and loss of functional transporters (Baumann et al., 2007; Fleckenstein et al., 2007). Thus, transporter substrates and blockers display critical differences in their acute and long-term effects.

Several studies have reported that mephedrone and methylone inhibit the uptake of monoamine neurotransmitters in brain tissue and in cells, suggesting these two cathinones function as transporter blockers (Cozzi et al., 1999; Hadlock et al., 2011; Lopez-Arnau et al., 2012; Martinez-Clemente et al., 2012; Simmler et al., in press). Data from our laboratory, summarized in Table 1, confirm that mephedrone and methylone block the uptake of [^{3}H]dopamine, [^{3}H]norepinephrine and [^{3}H]serotonin into rat brain synaptosomes (Baumann et al., in press). However, it must be clarified that traditional uptake-inhibition assays cannot discriminate between drugs acting as transporter substrates versus those acting as blockers, since both types of drugs prevent the accumulation of [^{3}H]neurotransmitters into tissue. To address this problem, we and others have developed in vitro release assays in rat brain synaptosomes which can distinguish between these two types of drugs (Nagai et al., 2007; Rothman and Baumann, 2003; Rothman et al., 2001).

Results from release assays reveal that mephedrone and methylone function as substrates at monoamine transporters, thereby stimulating the release of [^{3}H]1-methyl-4-phenylpyridinium ([^{3}H]MPP+) via DAT and NET, and release of [^{3}H]serotonin via SERT (Baumann et al., 2012; Nagai et al., 2007). The data in Table 1 show that mephedrone, methylone, and MDMA are non-selective transporter substrates (i.e., non-selective releasers), while amphetamine is a selective substrate at DAT and NET. Mephedrone displays similar releasing potency at all three transporters and is about twice as potent as methylone. Mephedrone, methylone, MDMA, and amphetamine are fully efficacious in the release assays (i.e., E_{max} close to 100%), while MDPV and cocaine are inactive as releasers. The findings from assays using synaptosomes are consistent with the evidence demonstrating mephedrone and methylone function as transportable substrates in assays utilizing transfected cells expressing human DAT, NET and SERT (Eshleman et al., unpublished; Simmler et al., in press).

Recent data from our laboratory and others reveal that MDPV displays a novel pharmacological profile when compared to other bath salts cathinones (Baumann et al., in press; Simmler et al., in press). Specifically, MDPV is a potent uptake blocker at DAT and NET with no measurable substrate activity (see Table 1). The transporter blocking properties of MDPV are analogous to those of the structurally-related compound pyrovalerone (Heron et al., 1994; Meltzer et al., 2006). When compared to the prototypical transporter blocker cocaine: MDPV is 50-fold more potent at DAT, 10-fold more potent at NET, and 10-fold less potent at SERT. Taken together, the in vitro results indicate that mephedrone and methylone are non-selective transporter substrates, whereas MDPV is a pure catecholamine-selective transporter blocker.

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