Symposium

Bath Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines

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The abuse of synthetic psychoactive substances known as "designer drugs," or "new psychoactive substances" (NPS), is increasing at an alarming rate. NPS are purchased as alternatives to traditional illicit drugs of abuse and are manufactured to circumvent laws regulating the sale and use of controlled substances. Synthetic cathinones (i.e., "bath salts") and synthetic cannabinoids (i.e., "spice") are two types of NPS that have received substantial media attention. Although low recreational doses of bath salts or spice compounds can produce desirable effects, high doses or chronic exposure often leads to dangerous medical consequences, including psychosis, violent behaviors, tachycardia, hyperthermia, and even death. Despite the popularity of NPS, there is a paucity of scientific data about these drugs. Here we provide a brief up-to-date review describing the mechanisms of action and neurobiological effects of synthetic cathinones and cannabinoids.

Introduction

Over the past few years, there has been an alarming increase in the abuse of synthetic psychoactive substances known as "designer drugs" or "legal highs" (Rosenbaum et al., 2012; Johnson et al., 2013; Nelson et al., 2014). These substances are purchased as alternatives to traditional illicit drugs of abuse and are manufactured to intentionally circumvent the laws regulating the sale and use of controlled substances. Countries of the European Union have adopted the term "new psychoactive substances" (NPS) to denote this category of emerging drugs, and we will use this nomenclature here (Brandt et al., 2014). NPS are synthesized by clandestine chemists who hijack the medical and patent literature to identify compounds targeting specific transporters or receptors implicated in the effects of psychoactive drugs (Collins, 2011; Lewin et al., 2014). Internet sales and marketing have made NPS easily available on a global scale. Synthetic cathinones (i.e., "bath salts") and synthetic cannabinoids (i.e., "spice") are two types of NPS that have received substantial media attention. Synthetic cathinones produce amphetamine- or cocaine-like subjective effects by activating monoamine systems in the brain and periphery (Baumann et al., 2013a; De Felice et al., 2014), whereas synthetic cannabinoids produce marijuana-like effects by activating the endocannabinoid system (Fattore and Fratta, 2011; Wiley et al., 2014a). Low recreational doses of bath salts or spice compounds produce the expected desirable effects, but high doses or chronic exposure can lead to dangerous medical consequences, including psychosis, violent behaviors, tachycardia, hyperthermia, and even death (Prosser and Nelson, 2012; Hermanns-Clausen et al., 2013; Kronstrand et al., 2013).

Because of the public health risks posed by NPS, the governments of many countries, including the United States, have passed legislation to ban the sale, possession, and use of specific synthetic cathinones and cannabinoids (Drug Enforcement Administration, 2011, 2013; German et al., 2014). Unfortunately, such legislation has fostered the emergence of new "replacement" analogs that are manufactured to skirt regulatory control, and this trend is expected to continue (Shanks et al., 2012; Seely et al., 2013). Very little information is available regarding the mechanisms of action, pharmacological effects, and toxicological profile for most NPS. The present brief review is based upon the minisymposium, "Bath Salts, Spice and Related Designer Drugs: The Science Behind the Headlines," presented at the Society for Neuroscience annual meeting held in Washington, DC in 2014. Here we aim to provide the most up-to-date information about the pharmacology of synthetic cathinones and cannabinoids, with a specific focus on the neurobiology of these agents.

"Bath salts" cathinones interact with monoamine transporters

Psychoactive "bath salts" first appeared in the recreational drug marketplace of the United States during late 2010. By early 2011, there was a dramatic spike in reports of bath salts overdose to poison control centers and an influx of patients admitted to emergency departments with toxic exposures (Spiller et al., 2011;

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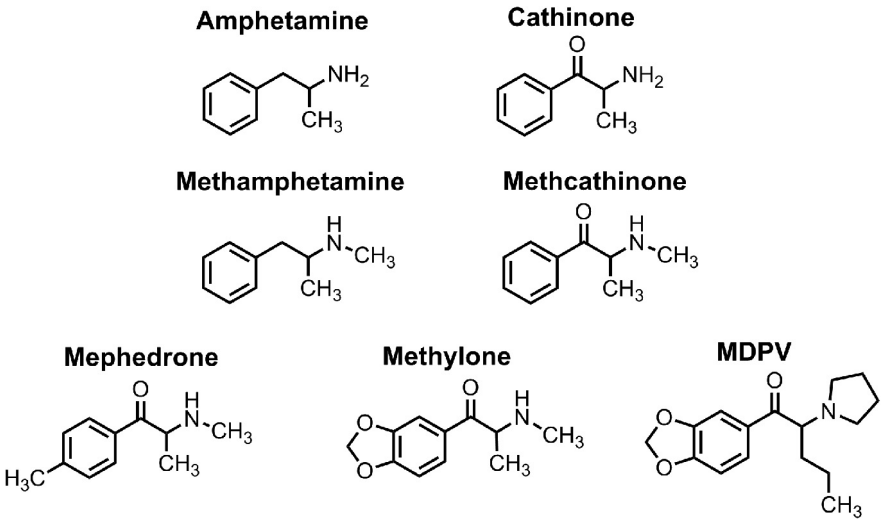

Figure 1. Chemical structures of synthetic cathinones found in bath salts NPS and their relationship to the plant-derived compound cathinone.

Ross et al., 2012). Patients intoxicated with bath salts can display severe symptoms, including psychosis, hallucinations, agitation, tachycardia, hypertension, and hyperthermia, often accompanied by combative or violent behaviors. Forensic analysis of bath salts products revealed the presence of three main synthetic cathinones, depicted in Figure 1: 4-methyl-*N*-methylcathinone (mephedrone), 3,4-methylenedioxy-*N*-methylcathinone (methylone), and 3,4-methylenedioxypyrovalerone (MDPV) (Spiller et al., 2011; Shanks et al., 2012). These compounds are structurally related to the parent compound cathinone, which is a naturally occurring β-keto amphetamine with known psychostimulant properties (Schechter and Glennon, 1985; Kalix and Glennon, 1986). Some bath salts powders consist of relatively pure preparations of one synthetic cathinone, but others contain mixtures of two or more different cathinones, along with adulterants, including caffeine, lidocaine, or piperazines (Davies et al., 2010; Zawilska and Wojcieszak, 2013). Like other stimulant drugs, synthetic cathinones target monoamine transporters expressed on nerve cells and other cell types (Hadlock et al., 2011; López-Arnau et al., 2012; Martínez-Clemente et al., 2012). Monoamine transporters are members of the SLC6 solute carrier family of proteins that mediate the sodium-dependent uptake of monoamine neurotransmitters, and there are specific transporters for norepinephrine (NET), dopamine (DAT), and 5-HT (SERT) (Kristensen et al., 2011). Drugs that interact with transporters can be divided into two types: (1) amphetamine-like substrates or (2) cocaine-like blockers (Rothman and Baumann, 2003; Sitte and Freissmuth, 2010). Both types of drugs increase extracellular concentrations of monoamines, but substrates induce transporter-mediated inward currents (i.e., depolarization) and transmitter efflux (i.e., release), whereas blockers do not. Additionally, the transporter selectivity for a given drug is predictive of behavioral effects because drugs that are selective for DAT are powerful locomotor stimulants, but drugs selective for SERT are not (Rothman and Baumann, 2006; Howell and Kimmel, 2008).

Several research groups have examined the interaction of synthetic cathinones with monoamine transporters using a variety of methods. In rat brain synaptosomes, mephedrone and methylone are nonselective transporter substrates, thereby evoking the release of preloaded [^{3}H]neurotransmitters at DAT, NET, and SERT (Baumann et al., 2012). The effects of mephedrone and methylone in synaptosomes mimic those of the illicit drug 3,4-methylenedioxymethamphetamine (MDMA). By contrast, MDPV is a transporter blocker that potently inhibits [^{3}H]neurotransmitter uptake at DAT and NET, with little effect at SERT (Baumann et al., 2013b). Importantly, MDPV is 50 and 10 times more potent than cocaine as a blocker at DAT and NET, respectively. Although studies in synaptosomes provide the advantage of high-throughput drug screening in native tissue, experiments in cells allow more detailed assessment of drug–transporter interactions. Assay systems using human transporters expressed in HEK293 cells show that mephedrone, methylone, and other ring-substituted cathinones are substrates at hDAT, hNET, and hSERT, whereas MDPV is a potent blocker at hDAT and hNET only (Eshleman et al., 2013; Simmler et al., 2013, 2014). Thus, results from human transporters are consistent with results from rat brain synaptosomes. Perhaps the most sophisticated method for examining drug–transporter interactions involves the measurement of transporter-mediated ionic currents using voltage-clamp techniques in cells expressing human transporters (Sonders et al., 1997; Sitte et al., 1998; De Felice et al., 2014). An electrophysiological signature provides definitive information about the mechanism of drug action at the molecular level. Because substrates are translocated through the transporter along with sodium ions, these agents produce transporter-mediated inward currents. Blockers bind to the transporter but are not translocated, so these agents produce outward currents (due to block of an endogenous leak current). As specific examples, amphetamine and mephedrone induce hDAT-mediated inward currents, whereas cocaine and MDPV induce outward currents (Cameron et al., 2013a, b; Kolanos et al., 2013). Together, the data from several lines of evidence agree that ring-substituted cathinones, such as mephedrone and methylone, are nonselective transporter substrates. MDPV is not a transporter substrate, most likely because the drug molecule is too large to fit through the transporter, but acts as a potent blocker at DAT and NET with minimal activity at SERT.

Synthetic cathinones induce stimulant effects in laboratory rodents

Consistent with their activity as transporter substrates and blockers, synthetic cathinones increase monoamine transmission in laboratory rodents. *In vivo* microdialysis studies in rats demonstrate that mephedrone and methylone elevate extracellular concentrations of dopamine and 5-HT in the nucleus accumbens, whereas MDPV increases dopamine without affecting 5-HT (Kehr et al., 2011; Baumann et al., 2012, 2013b; Wright et al., 2012). All synthetic cathinones investigated to date produce dose-dependent stimulation of motor activity when administered to rats or mice (Lisek et al., 2012; López-Arnau et al., 2012; Marusich et al., 2012, 2014; Baumann et al., 2013b; Fantegrossi et al., 2013; Gatch et al., 2013), probably due to enhancement of dopamine transmission. Most studies agree that MDPV is 3–10 times more potent than mephedrone or methylone as a locomotor stimulant. As noted above, bath salts products may contain a

number of different cathinones, yet MDPV is the chief compound found in blood and urine from fatal cases of bath salts overdose in the United States (Spiller et al., 2011; Murray et al., 2012; Kesha et al., 2013; Wyman et al., 2013). This intriguing observation suggests that MDPV is the chief culprit involved with adverse effects of bath salts. It is tempting to speculate that potent blockade of DAT by MDPV is responsible for neurological symptoms and hyperthermia in bath salts overdose cases, whereas blockade of NET could underlie cardiovascular stimulation. Determining the pharmacokinetics and metabolism of synthetic cathinones in rodent models is essential because clinical data are limited to isolated forensic cases. Mephedrone and methylone are extensively metabolized in the rat (Kamata et al., 2006; López-Arnau et al., 2013; Martínez-Clemente et al., 2013), but the potential bioactivity of various identified metabolites has not been well studied. It is noteworthy that methylone and MDPV possess a 3,4-methylenedioxy ring-substitution akin to the illicit drug MDMA, a compound that displays nonlinear kinetics in rodents and humans (de la Torre et al., 2000; Kolbrich et al., 2008; Baumann et al., 2009; Fantegrossi et al., 2009; Concheiro et al., 2014). The phenomenon of nonlinear kinetics is characterized by greater-than-predicted plasma concentrations of MDMA due to autoinhibition of drug metabolism (Heydari et al., 2004; de la Torre et al., 2004). Similar to MDMA, MDPV is metabolized by *O*-demethylenation, thereby producing the ring-hydroxylated metabolites, 3,4-dihydroxypyrovalerone and 4-hydroxy-3-methoxypyrovalerone (Meyer et al., 2010; Strano-Rossi et al., 2010; Anizan et al., 2014). 3,4-Dihyhdroxypyrovalerone is a potent blocker of DAT and NET (Meltzer et al., 2006), so this metabolite could contribute significantly to the *in vivo* pharmacology of MDPV. 4-Hydroxy-3-methoxypyrovalerone is a long-lasting metabolite that may prove useful for forensic validation of MDPV exposure in human subjects (Anizan et al., 2014). Whether methylone and MDPV display nonlinear kinetics similar to MDMA is an unresolved issue that warrants investigation. No controlled clinical–laboratory studies with synthetic cathinones have been performed, and such studies are needed to understand the complex pharmacology of these drugs in humans.

Synthetic cathinones have abuse liability in rodent models

Recently, the addictive potential of synthetic cathinones has been investigated in rodent models. In preclinical abuse liability studies, the intravenous self-administration model is considered the "gold standard" because of its high degree of face and predictive validity (Watterson et al., 2013). From a neurobiological perspective, stimulation of mesolimbic dopamine transmission is a key mechanism underlying drug self-administration behavior (Willuhn et al., 2010; Espana and Jones, 2013). In the self-administration procedure, rats fitted with indwelling jugular catheters are placed in operant chambers equipped with two levers. Presses on the "active" lever result in a computer-controlled intravenous drug infusion and simultaneous presentation of a stimulus complex (light + tone). Presses on the other lever (i.e., "inactive") produce no consequences but are recorded as a measure of nonspecific behaviors. Comparisons between MDPV and methylone in the self-administration model are of interest because these drugs have structural similarity but differ in their mechanism of action and selectivity for DAT versus SERT (see above). For MDPV, rats readily acquire self-administration across a range of doses (0.05–0.5 mg/kg/infusion) (Aarde et al., 2013a; Watterson et al., 2014). Under a progressive ratio schedule of reinforcement, in which the number of lever presses for drug infusion increases exponentially with each successive infusion, MDPV breakpoints are positively correlated with drug dose (Watterson et al., 2014). Moreover, MDPV breakpoints are similar to those produced by methamphetamine at the same dose (0.05 mg/kg/infusion). Escalation of MDPV intake is observed at 0.1 and 0.2 mg/kg/infusion doses across 6 h access sessions. This escalation of intake is similar in magnitude to that observed with 0.05 mg/kg/infusion of methamphetamine and is typically seen with other drugs that support compulsive use in humans (e.g., cocaine and heroin). For methylone, rats display self-administration across a range of doses (0.1–0.5 mg/kg/infusion) (Watterson et al., 2012). As with MDPV, a positive relationship between methylone dose and breakpoints is observed under progressive ratio conditions. However, unlike MDPV, escalation of drug intake is not observed with methylone. These data suggest that the serotonergic effects of methylone may dampen certain reinforcing properties of the drug. Nevertheless, under some conditions, rats will self-administer methylone to the point of convulsions and death, highlighting the dangers of synthetic cathinone use and corroborating reports of methylone-associated deaths in humans (Cawrse et al., 2012; Pearson et al., 2012). Overall, the available evidence shows that MDPV and methylone are readily self-administered by laboratory rats, and these findings agree with reports showing that mephedrone is also self-administered by rats (Hadlock et al., 2011; Aarde et al., 2013b; Motbey et al., 2013). Escalation of drug intake, a cardinal feature of drug addiction, is observed in laboratory rodents self-administering certain synthetic cathinones. Together, these preclinical studies suggest a high abuse potential for synthetic cathinones, such as MDPV, methylone, and mephedrone.

"Spice" cannabinoids interact with the endocannabinoid system

Plant-derived phytocannabinoids (e.g., Δ^9-tetrahydrocannabinol [THC]) and synthetic cannabinoids produce their psychoactive effects through activation of the endocannabinoid system in the brain. This neuromodulatory system is comprised of two identified receptors (CB_1 in the brain and periphery, and CB_2 primarily in the periphery), at least two endogenous ligands (anandamide and 2-arachidonoyl glycerol), and associated synthetic and metabolic enzymes (for review, see Pertwee, 2008). Discovered in the late 1980s and early 1990s (Devane et al., 1988, 1992; Matsuda et al., 1990), the endocannabinoid system contributes to a number of physiological and pathological processes, including appetite, pain, mental illness, reward, and neurodegenerative diseases (Berry and Mechoulam, 2002; Mechoulam et al., 2002; Walker and Huang, 2002; van der Stelt and Di Marzo, 2003; Di Marzo et al., 2004). Development of the first research cannabinoid compounds that would later appear in products confiscated from drug users also occurred during this time span (Huffman et al., 1994; Lainton et al., 1995), although illicit diversion of these compounds did not occur until the early 2000s. The primary goals of the original research were to identify and differentiate structural properties of the newly discovered CB_1 and CB_2 receptors (Huffman, 2000, 2005; Huffman and Padgett, 2005; Huffman et al., 2005), but the purpose of currently available cannabinoid NPS is to achieve a marijuana-like intoxication. Compared with marijuana, however, abuse of these synthetic substances is associated with a higher prevalence of severe adverse effects, such as hypertension, tachycardia, hallucinations, agitation, seizures, and panic attacks that often require immediate medical care (Seely et al., 2012; Fantegrossi et al., 2014).

The broad structural diversity of cannabinoid agonists was recognized early, as observed in the array of structurally distinct

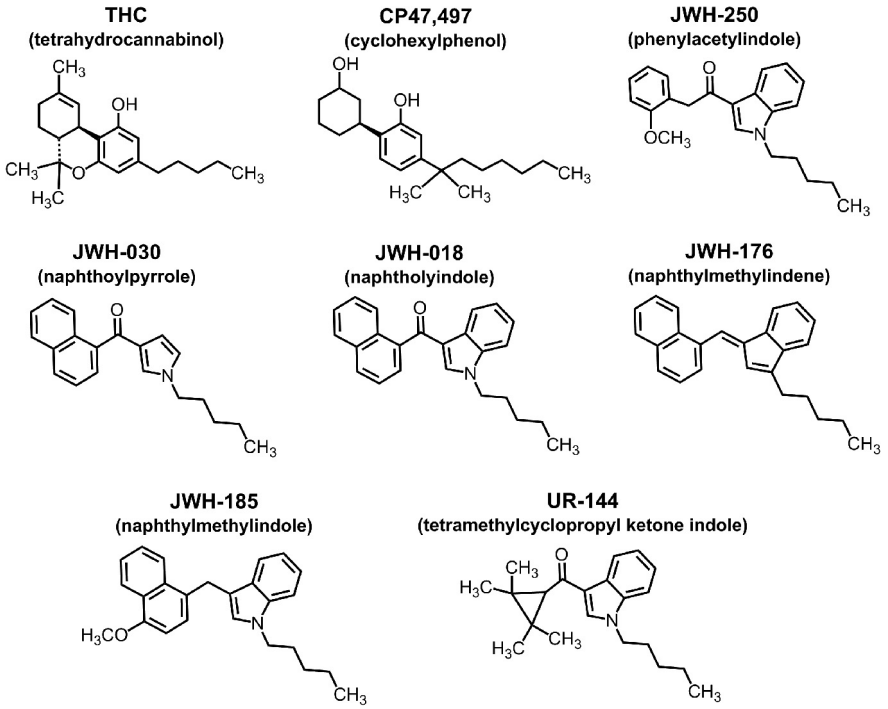

Figure 2. Chemical structures of synthetic cannabinoids found in spice NPS and their relationship to the plant-derived compound THC.

classes of compounds that produce cannabinoid activity, including tetrahydrocannabinols, bicyclic cannabinoids, aminoalkylindoles, and anandamide analogs. WIN55212-2, an aminoalkylindole, was the template for synthesis of the original series of indole-derived synthetic cannabinoids (Eissenstat et al., 1995; Wiley et al., 2011). Subsequent studies reported an orderly structure–activity relationship between structural variation in these molecules (e.g., length and branching of the chain) and cannabinoid binding (Huffman et al., 1994; Lainton et al., 1995; Aung et al., 2000) and, when tested, *in vivo* cannabimimetic activity (Wiley et al., 1998, 2012a, b, 2014a). Interestingly, some of the compounds in this series with the best CB_1 receptor affinities are the ones that were identified in earliest "spice" products, demonstrating that clandestine chemists are mining the scientific literature to guide manufacture.

Yet, despite similarity to THC in much of its pharmacology, WIN55212-2 differs from other classes of cannabinoids in its molecular interactions with cannabinoid receptors, having at least one unique site of attachment that is not shared by other cannabinoid agonists or by the CB_1 antagonist rimonabant (Petitet et al., 1996; Song and Bonner, 1996). In addition, WIN55212-2 has higher affinity for peripheral cannabinoid CB_2 receptors than for CB_1 receptors in the brain (Showalter et al., 1996), a property it shares with many of the synthetic cannabinoids that have been identified in confiscated NPS (Huffman and Padgett, 2005; Manera et al., 2008). Because the physiological functions of CB_2 receptors are not completely understood, it is possible that agonist action at these receptors may modulate the pharmacological profile of WIN55212-2 and other indoles. In addition, WIN55212-2 and many other indole-derived cannabinoids are full agonists at CB_1 receptors, compared with the weak partial agonist activity of THC (Atwood et al., 2011; Brents et al., 2011, 2012; Chimalakonda et al., 2012). Finally, several lines of research have suggested that WIN55212-2 (and perhaps other structurally related synthetic cannabinoids) interacts with non-cannabinoid receptors in the brain (Breivogel et al., 2001; Hájos et al., 2001; Monory et al., 2002). These actions may, in turn, modulate *in vivo* drug effects, leading to unexpected psychoactive effects and peripheral toxicities.

As of 2009, the most prevalent synthetic cannabinoids identified in spice or herbal incense products were classified into seven structural groups, as depicted in Figure 2: naphthoylindoles (e.g., JWH-018, JWH-073, AM-2201), naphthylmethylindoles (JWH-185), naphthoylpyrroles (JWH-030), naphthylmethylindenes (JWH-176), phenylacetylindoles (JWH-250, RCS-4), cyclohexylphenols (CP47,497), and tetrahydrocannabinols (Δ^9-THC, HU-210) (European Monitoring Centre for Drugs and Drug Addiction, 2010); however, increased legal restriction has resulted in exploitation of new structural motifs from the scientific literature or led to the invention of new structures. For example, after the United States Drug Enforcement Administration banned JWH-018 and other naphthoylindoles, novel tetramethylcyclopropyl ketone indoles (UR-144, XLR-11) started being identified in confiscated products (Fig. 2). The sheer number of possible combinations of structural constituents is staggering and complicates prediction of which NPS are likely to be included in the next round of "product."

Synthetic cannabinoids display complex pharmacokinetics and metabolism

In addition to the obvious risk of using compounds with unknown pharmacological properties, synthetic cannabinoids have an additional set of potential risks associated with exposure to pyrolytic byproducts of the compound or the plant material on which it is sprayed (because smoking is the normal route of administration) (Kavanagh et al., 2013), biotransformation to active metabolites, and shared metabolic pathways with commonly used medications, which may lead to drug–drug interactions. Despite the popular use of these substances, little is known about their pharmacokinetics or their *in vivo* pharmacology and toxicology. The few published pharmacokinetic studies have shown that, like phytocannabinoids, synthetic cannabinoids are highly lipophilic and the parent compounds readily cross the blood–brain-barrier and are distributed to areas high in CB_1 receptor density (Dhawan et al., 2006; Wiebelhaus et al., 2012). Whereas THC has only one major psychoactive Phase I metabolite (11-hydroxy-THC) (Huestis et al., 1992), metabolism of synthetic cannabinoids can proceed via several pathways, resulting in multiple metabolites. Earlier studies reported that several Phase I hydroxylated metabolites of AM2201 (Chimalakonda et al., 2012), JWH-018 (Brents et al., 2011), and JWH-073 (Brents et al., 2012) retain high affinity for CB_1 receptors, often higher than that of THC. In addition, these metabolites exhibit a range of intrinsic efficacies at the CB_1 receptor, from neutral antagonists, to partial agonists, to full agonists. Importantly, *in vivo* studies demonstrate that these metabolites retain biological effects consistent with their *in vitro* profiles, in some cases suggesting that they continue to penetrate the brain, or are perhaps generated

within the brain. *In vitro* studies using human recombinant P450 enzymes identified CYP2C9 and CYP1A2 as major isoforms responsible for the generation of these hydroxylated metabolites, which can be detected in human blood and urine as glucuronic acid conjugates (Chimalakonda et al., 2011; Patton et al., 2013). Mechanistic studies have shown that selective inhibitors of CYP2C9 (sulfaphenazole) and CYP1A2 (α-naphthoflavone) block oxidation of JWH-018 and AM2201 in human liver microsomes (Chimalakonda et al., 2013), further demonstrating the importance of these P450 isoforms in the detoxification of these compounds. The *in vitro* evidence suggests that individuals with certain allelic variants for these enzymes might be more likely to experience increased toxicity following the use of synthetic cannabinoids. Urinary elimination of synthetic cannabinoids or their metabolites may contribute to the kidney toxicity that has been observed with some of these compounds (Sobolevsky et al., 2010; Moran et al., 2011; Centers for Disease and Prevention, 2013).

Given their shared metabolism via P450 isoforms, combined use of synthetic cannabinoids and various prescription medications may result in adverse drug–drug reactions. Commonly prescribed drugs, such as valproic acid and sertraline potently inhibit CYP2C9, whereas drugs, such as ciprofloxacin and fluvoxamine, strongly inhibit CYP1A2. Additionally, CYP2C9 is a major polymorphic enzyme (Paine et al., 2006) and is responsible for the metabolism of a number of clinically important drugs, such as warfarin, phenytoin, tolbutamide, losartan, and ibuprofen. More than five allelic variants have been identified, including two "loss of function" variants (CYP2C9*4 and CYP2C9*5) (Seng and Seng, 2008). Similarly, CYP1A2 is responsible for the metabolism of numerous psychiatric medications, including olanzapine, clozapine, haloperidol, thioridazine, imipramine, clomipramine, fluvoxamine, and tacrine (Shirley et al., 2003) but is well conserved without common functional polymorphisms (Hiratsuka, 2012). Hence, the possibility of drug–drug interactions is a serious consideration using synthetic cannabinoids.

Synthetic cannabinoids produce THC-like stimulus effects in animal models

To the extent that synthetic cannabinoids have been evaluated *in vivo*, they share the capacity of THC to produce a tetrad of diagnostic effects: locomotor suppression, antinociception, hypothermia, and catalepsy (Wiley et al., 2014a). Synthetic cannabinoids also engender THC-like discriminative stimulus effects in rodents and nonhuman primates (Wiley et al., 1995; Wiley et al., 1998). Unlike the situation with synthetic cathinones, a robust model of intravenous THC self-administration in rodents has not been established, although self-administration has been reported in squirrel monkeys (Tanda et al., 2000; Justinova et al., 2003). WIN55212-2 self-administration has been reported in rodents (Fattore et al., 2001; Deiana et al., 2007); however, its usefulness as a screening tool for identification of synthetic cannabinoids likely to be abused has been disputed (Lefever et al., 2014). Consequently, THC discrimination in animal models remains the most pharmacologically selective method for assessing the likelihood that novel compounds will produce marijuana-like subjective effects in humans (Balster and Prescott, 1992). Animals used in drug discrimination learn to associate the interoceptive cues produced by THC or vehicle with one of two responses. For example, to receive food reinforcement, the animal must press a lever on the right side of the test chamber if an injection of THC was given before the session. If a THC injection was not given (e.g., vehicle injection), the animal must respond on the left lever to receive food. After the discrimination is established, other compounds are administered to determine whether they produce interoceptive cues similar to those produced by THC. Early research found that a number of naphthoylindoles, naphthylmethylindoles, and naphthoylpyrroles produce cannabinoid effects in rats or rhesus monkeys trained to discriminate THC or CP55940 from vehicle (Wiley et al., 1995, 1998). Later studies confirmed these results with other naphthoylindoles (JWH-018, JWH-073, and AM5983) (Järbe et al., 2010, 2011, 2014; Ginsburg et al., 2012; Marusich et al., 2013) and extended them to other classes of indole-derived cannabinoids, including phenylacetylindoles (Vann et al., 2009; Järbe et al., 2011) and tetramethylcyclopropyl ketone indoles (UR-144, XLR-11) (Wiley et al., 2013). In studies where more than one compound has been evaluated, the rank order of drug potency parallels CB_1 affinity, with compounds showing the highest affinity for CB_1 also showing the highest potency in drug discrimination. Reversal by the CB_1 antagonist rimonabant provides further verification that CB_1 receptors mediate the THC-like discriminative stimulus effects of synthetic cannabinoids (Järbe et al., 2011; Ginsburg et al., 2012). In the context of a THC discrimination procedure, cross-tolerance of THC and synthetic cannabinoids (CP55940, JWH-018, and JWH-073) has also been demonstrated in rhesus monkeys chronically treated with THC (Hruba et al., 2012). More recently, cross-substitution of THC and synthetic cannabinoids has been reported in separate groups of rodents trained to discriminate THC or JWH-018 from vehicle (Wiley et al., 2014b). To the limited extent to which they have been assessed, sex differences in the discriminative stimulus effects of synthetic cannabinoids are not apparent (J.L.W. and J.A.M., unpublished data). Finally, the duration of action of some synthetic cannabinoids in drug discrimination has been reported to be shorter than that of THC (Ginsburg et al., 2012), suggesting that the synthetic drugs may be administered more frequently with resultant enhancement of abuse potential.

Conclusions

In conclusion, this brief review has summarized the latest scientific data on the neurobiology of synthetic stimulants and cannabinoids. The available information suggests that most of these NPS resemble their progenitors (i.e., stimulants and THC) in their basic pharmacology, but these substances may have unexpected toxicological effects related to factors, such as dosage, efficacy, or active metabolites, which remain largely unexplored because most mechanistic research has focused on the stimulant actions of cathinones and cannabimimetic effects of synthetic cannabinoids. Potential "off-target" sites of action for most NPS are not known. This paucity of scientific knowledge is in direct contrast to the widespread availability of peer-to-peer information and access via the Internet and other electronic media, particularly for adolescents (Wax, 2002; Castellanos et al., 2011). Despite an alarming increase in the number of people seeking medical attention following use of NPS (Spiller et al., 2011; Centers for Disease and Prevention, 2011; Harris and Brown, 2013; Helander et al., 2014), the actual incidence of use is probably still underestimated because tracking continues to be difficult, partially due to inadequacy of detecting most substances. Meanwhile, the number of new "replacement" cathinones and cannabinoids continues to grow. The challenge for scientists, clinicians, and policymakers is to discover creative and effective ways to maximize their efforts in responding to this rapidly changing drug landscape.

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