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HIV/AIDS AND ADDICTION (P LEVOUNIS, SECTION EDITOR)

Psychostimulant Abuse and HIV Infection: Cocaine, Methamphetamine, and 'Bath Salts' Cathinone Analogs

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Abstract Psychostimulants are among the most widely-abused substances worldwide, and typically exert their abuse-related effects via interactions with monoamine reuptake transporters within the central nervous system. Over the last decade, a symbiotic relationship between psychostimulant abuse and HIV infection has been demonstrated, where psychostimulants potentiate the effects of HIV infection, and HIV infection increases sensitivity to psychostimulant drugs. Most recently, a new class of designer psychostimulants has emerged in abuse-ready 'bath salt' preparations. These commercial products typically contain ring-substituted and/or side-chain-substituted analogs of cathinone, which is itself a psychostimulant drug of abuse in its natural plant form. The cathinone analogs exhibit a range of interactions with monoamine transporters, from cocaine-like reuptake inhibition to methamphetamine-like release. Since the primary mechanism of action of these novel drugs overlaps with those of traditional psychostimulants, it may be the case that the cathinone analogs also interact with HIV infection. As use of these emerging cathinone-derived drugs continues to rise, there is an urgent need to better understand the pharmacology and toxicology of these novel compounds, both in terms of their abuse-related effects and in terms of their capacity to interact with HIV infection.

Keywords Monoamine reuptake transporters · CNS · Cathinone-derived drugs · Pharmacology · Toxicology

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Introduction

Human immunodeficiency virus (HIV) is a sexually transmitted infection that currently affects approximately 1.2 million people in the US, one in five of whom are unaware of their infection [1]. As of December 2012, an estimated 33.5 million people were infected with HIV worldwide, and there is little to no indication that incidence rates are decreasing [2]. Classically, HIV infection is defined as a progressive loss of CD4+ T lymphocytes, leading to the inability to mount an immune response against opportunistic infections and, ultimately, death [3]. Infection with HIV can lead to multiple physiological effects aside from immunosuppression, including neurological complications in later stages of the infection such as HIV-associated dementia [4••, 5]. Infection of the brain caused by the retrovirus associated with HIV infection, HIV-1, is commonly referred to as neuroAIDS and can develop into a chronic neurological disorder known as HIV-1-associated dementia (HAD) or various stages of neurocognitive impairments known as HIV-1-associated neurocognitive disorders (HAND). Attention deficits, impaired short-term memory, compromised fine motor skills, tremors, and slowness of movements have all been associated with HAD, while symptoms of HAND can range from undetectable impairment to encephalitis and dementia [6••].

HIV infection occurs when glycoproteins found on the HIV-1 retrovirus envelope (commonly gp120) interact with cell surface markers on immune cells, allowing for fusion of the viral and host membranes and the subsequent release of the viral core into the host immune cell. In the central nervous system (CNS), the surface markers implicated in the progression of HIV infection via interaction with HIV-1 glycoprotein interaction include CD4+ T lymphocytes, monocytes, macrophages, and microglia [3]. The extracellular interactions of gp120 lead to a variety of intracellular signaling mechanisms, including activation of transcription factors, such as the

nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB, which signals the release of pro-inflammatory cytokines and chemokines [7, 8]. An influx of inflammatory cytokines and chemokines generated by an HIV-infected immune cell increases activation and ultimately infection of neighboring immune cells [7]. Oxidative stress, secretion of neurotoxins (including quinolinic acid and arachidonic acid metabolites), and release of HIV proteins such as transcriptional transactivator (Tat) often accompany HIV infection as well [9, 10••].

Several illicit drugs are also known to cause neuronal dysfunctions that can lead to neurocognitive deficiencies, and use of these substances can accelerate neurotoxin release [10••]. For example, methamphetamine (METH) elicits neurotoxicity by binding to the dopamine transporter (DAT) and reversing its function. In other words, METH forces the DAT to abandon its normal physiological function as a reuptake transporter for synaptic dopamine (DA), and instead causes it to release excess DA into the synapse [11, 12]. This reversal elicits persistent changes in striatal DAT expression [12]. Once METH is in the nerve terminal, it reverses the vesicular monoamine transporter (VMAT), forcing DA to be released from synaptic vesicles and generating a large pool of cytosolic DA for DAT to transport into the synapse [11, 13]. As with DAT, persistent changes in VMAT expression are also observed [14]. Additionally, METH drastically reduces concentrations of the DA precursor tyrosine hydroxylase (TH), further depleting DA stores in the striatum. However, the neurotoxic effects of METH extend beyond the dopaminergic system. One major downstream effect of METH use is glutamate excitotoxicity, as evidenced by the upregulation of both AMPA and NMDA receptors in the hippocampus following high-dose METH use [15]. In addition to dopaminergic and glutamatergic toxicities, METH can generate reactive oxygen and nitrogen species, via oxidation/metabolism of DA and increased nitric oxide synthase activity [16–18].

Because psychoactive drugs of abuse and HIV both have CNS toxic effects, comorbidity is a concern. Many behavioral risk factors result in the propagation of HIV, but injection drug use is the second most common behavior directly associated with HIV transmission in the US [4••]. Injection drug use directly accounted for one-third of the total number of acquired immunodeficiency syndrome (AIDS) cases in the US through 2002, and the National Institute on Drug Abuse (NIDA) also acknowledges that drug abuse (regardless of route of administration) can interfere with sexual judgment, indirectly leading to HIV transmission through sexual intercourse [19]. Thus, drug abuse can propagate HIV infection, both directly and indirectly. Not only can drugs of abuse potentiate the effects of HIV infection, but the reverse appears to be true as well, as evidence suggests HIV infection can increase preference and sensitivity to certain drugs of abuse, thus implying the relationship between HIV and drug abuse is symbiotic.

Psychostimulants

In combination with HIV, one class of abused drugs—the psychostimulants—has been shown to lead to glial and neuronal injury and/or death [4••]. Psychostimulants are drugs capable of producing a variety of effects in humans, including increased energy, decreased need for sleep, cardiovascular stimulation, and elevated mood. In animals, these drugs increase locomotor activity, increase heart rate and blood pressure, and are readily self-administered due to their powerful reinforcing properties. Most psychostimulants are known to interact with the DAT, norepinephrine transporter (NET), serotonin transporter (SERT), and VMAT in the CNS. In general, drugs that target transporter proteins can be divided into two classes based on their precise mechanism of action. The first class is comprised of the passive monoamine reuptake inhibitors, exemplified by cocaine (Fig. 1a), while the second class is comprised of transporter substrates/monoamine releasers, typified by METH (Fig. 1d) [20]. Reuptake inhibitors bind to monoamine transporter proteins, but are not themselves transported; instead, reuptake inhibitors elevate extracellular monoamine neurotransmitter concentrations by passively blocking transporter-mediated recapture of monoamines from the synapse. Cocaine, for example, binds with near-equal affinity to the DAT, SERT, and NET, but not all reuptake inhibitors have similar affinity for each transporter. On the other hand, substrate-type releasers such as amphetamine bind to transporter proteins and are subsequently transported into the cytoplasm of nerve terminals. Releasers elevate extracellular monoamine neurotransmitter concentrations by first promoting efflux of transmitter by a process of transporter-mediated exchange and second, by increasing cytosolic levels of monoamines by disrupting storage of transmitters in vesicles [21, 22]. This second step leads to increases in the amount of neurotransmitters available for release by transporter-mediated exchange. While the net result of elevated extracellular monoamine concentrations is the same for both of these two classes of psychostimulants, the differences between the underlying mechanisms of this synaptic overflow is likely responsible for some of the observed differences in overall drug effects.

Cocaine

As previously noted, cocaine is a psychostimulant which functions as a monoamine reuptake inhibitor. The number of HIV-infected patients that are also cocaine-abusers has been rising, and these individuals with concomitant cocaine abuse are often characterized by amplified disease severity and rapid progression to NeuroAIDS [23••]. Alone, cocaine enhances cell toxicity in astrocytes, enhances the inflammatory responses in microglia, and potentiates Tat-induced reactive

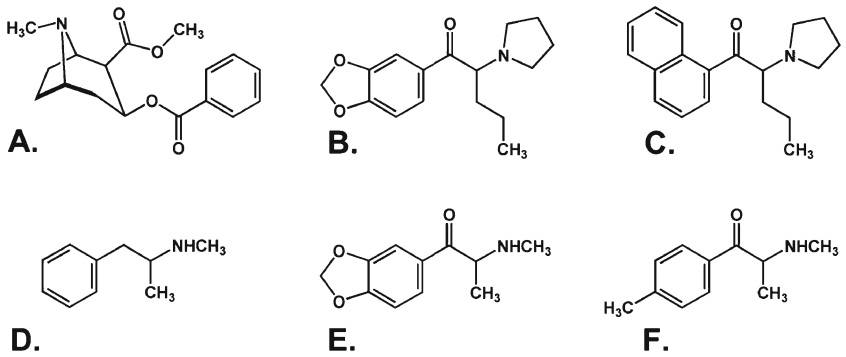

Fig. 1 Psychostimulant drugs of abuse. *Top row:* Monoamine reuptake inhibitors, including cocaine (**a**) and 'bath salt' constituents 3,4-methylenedioxypyrovalerone [MDPV] (**b**) and naphyrone (**c**) *Bottom row:* Monoamine transporter substrates/releasers, including methamphetamine (**d**) and 'bath salt' constituents methylone (**e**) and mephedrone (**f**). Note that all of the 'bath salts' drugs, regardless of mechanism of action, are phenethylamines which contain a ketone on the β-carbon, designating them as substituted cathinones

oxygen species (ROS) formation, but exhibits little neurotoxicity to dopaminergic systems [9]. However, in combination with HIV, cocaine increases blood-brain barrier (BBB) permeability, recruitment of inflammatory cells, and potentiates neurotoxicity induced by viral proteins resulting in neuronal damage [6••]. Additionally, HIV-infected females using cocaine display impaired anterior cingulate and prefrontal cortex function [24]. In the presence of gp120, cocaine causes a decline in cell viability mediated by both imbalanced mitochondrial membrane potential and increased intracellular ROS [25]. Repeated cocaine treatment has been shown to enhance HIV-1 Tat-induced cortical excitability via L-type calcium channel over-activation [26]. Mitogen-activated protein (MAP) kinases and their downstream targets have also been implicated in the neurotoxicity associated with cocaine use [6••]. Cocaine use raises mortality rates in HIV-infected individuals [6••], likely mediated via increased BBB permeability. Furthermore, evidence of a synergistic relationship between cocaine and HIV-1 on CD4+ T-cell apoptosis has been noted [27]. Cocaine abuse in HIV-1-infected individuals thus exerts deleterious effects on the CNS, resulting in exacerbated neuropathogenesis via multiple pathways.

Methamphetamine

METH is a prototypical substrate-releasing psychostimulant drug of abuse. As is the case with many psychostimulants, METH is associated with a greater incidence of risk-taking behaviors, such as sharing/using dirty needles, engaging in unprotected sexual intercourse, and exchanging sexual favors or unprotected sex for drugs and/or money, all of which may lead to HIV infection [28]. Recently, METH use in individuals infected with HIV has been shown to increase HIV viral replication in various immune cells [5, 29]. While the exact mechanisms underlying these observations is not known, multiple processes have been suggested to play a role. These potential processes include METH interaction with D1 receptors on the surface of HIV-infected macrophages inducing reverse transcriptase [30], activation of the HIV long terminal repeat (LTR) in monocytes and CD4+ T lymphocytes, and induction of NF-κB translocation to the nucleus, leading to the release of inflammatory cytokines [29]. Furthermore, METH use has been shown to potentiate the neurotoxic effects of HIV [4••, 5].

Microglial activation is a common term for the phenotypic changes of microglial cells in response to injury or pathological conditions of the brain, and can lead to increases in proliferation, migration, and production of pro-inflammatory cytokines and chemokines, as well as increased phagocytosis and hypertrophy. In rodent brains, METH has been shown to activate microglia [31, 32], and human METH abusers have shown increased binding of activated microglial radiotracer compared with control subjects [33]. The previously described METH-induced potentiation of HIV-related neurotoxicity may be the result of microglial activation because METH has been shown to directly induce HIV expression in human microglia cells through activation of NF-κB [34].

The relationship between METH and HIV does not appear to be a one-way street. Not only has METH been shown to affect the progression of HIV infection, HIV appears to affect both preference for and sensitivity to METH. Both METH and HIV induce neuropathological changes in brain areas associated with motivated behaviors, leading researchers to examine the relationship between HIV and the rewarding effects of METH. For example, increased expression of the HIV-associated glycoprotein gp120 resulted in increased preference for oral METH solutions compared with quinine solutions in choice assays, and also increased sensitivity to METH in conditioned place-preference assays [35]. These preclinical studies suggest that the abuse potential of METH may be higher in populations infected with HIV. Interestingly, recent experiments with high doses of METH on CD4+ T cells demonstrated inhibition of HIV-1 replication and also

Table 1 Interaction of psychostimulants with monoamine transporters

Drug	DAT		NET		SERT	
	Affinity	Release	Affinity	Release	Affinity	Release
Cocaine	0.28	>100	4.47	–	1.10	>100
Methamphetamine	1.85	1.56	4.28	NT	26.70	>33
MDPV	0.01	>100	0.08	–	2.86	>100
Mephedrone	3.40	3.75	>25	0.058	>30	5.98
Methylone	2.73	>100	>25	0.140	>30	>10
Naphyrone	0.04	>100	0.18	NT	0.18	>100

Affinity is expressed as K_i values (μM) and stimulation of monoamine release is expressed as EC_{50} values (μM). In both cases, smaller numbers represent higher affinity and greater potency, respectively. NET release data originally reported by Baumann et al. [38•]. All other data originally reported by Simmler et al. [40•]. *DAT* dopamine transporter, *NET* norepinephrine transport, *SERT* serotonin transporter, *MDPV* 3,4-methylenedioxypyrovalerone, *NT* compound was not tested, – indicates that a compound was inactive in that assay

upregulation of the cellular anti-HIV-1 microRNAs [36]. These new data highlight the complex relationship between METH and HIV-1 infection and stress the need for continued research.

'Bath Salts'

'Bath salts' are emerging psychostimulant-like drugs of abuse, and batches of these illicit products contain a variety of ring-substituted and side-chain-substituted analogs of plant-derived cathinone (β-ketophenethylamines). Cathinone is found in the khat (Catha edulis) plant, a slow-growing shrub that has been cultivated in the Arabian Peninsula and the horn of Africa for thousands of years. The leaves and stalks of the plant are chewed to stimulate alertness and motor activity, to decrease feelings of fatigue, and to induce euphoric effects. Like many other medicinal plants, khat contains several active chemical compounds, of which cathinone is the most active.

In the US, cathinone is considered a drug of abuse, and was regulated under Schedule I of the Controlled Substances Act by the US Drug Enforcement Administration in 1993. In recent years, illicit drug chemists have begun to create stable analogs of cathinone, which are typically marketed as 'bath salts'. These drugs are readily available online, and may also be for sale in commercial establishments such as convenience stores, truck stops, or in certain tobacco shops. These commercial preparations are sold in colorful packaging (often branded with names such as Vanilla Sky, Ivory Wave, or White Rush) and typically contain milligram to gram quantities of a white powder administered by inhalation, ingestion, or injection.

The structures of some of the more common 'bath salt' constituents are presented in Fig. 1. In vitro assays have suggested that some of these cathinone analogs, such as 3,4-methylenedioxypyrovalerone [MDPV] (Fig. 1b) and naphyrone (Fig. 1c), function similarly to cocaine as reuptake inhibitors at monoamine transporters, while others, such as methylone (Fig. 1e) and mephedrone (Fig. 1f), appear to be amphetamine-like and act as monoamine releasers [37•, 38•, 39, 40•]. The complexity of the chemical structure of these constituents appears to be related to their capacity to act as blockers or releasers, with the more complex molecules acting as blockers and the simpler compounds acting as substrates (Table 1). Although data on the link between the use of bath salts and HIV progression are not currently available, it is reasonable to assume that this emerging class of synthetic psychostimulants will follow a similar trend to the previously documented potentiation of HIV as seen with cocaine and METH because individual cathinone analogs also interact with monoamine transporters in precisely the same fashion. Thus, 'bath salt' constituents may also act in concert with HIV, leading to glial and neuronal toxicity greater in magnitude than the neurotoxicity observed with either the 'bath salt' constituents or HIV individually.

Conclusions

Much of our understanding of the symbiotic relationship between HIV infection and psychostimulant abuse has been based on studies involving either cocaine or METH. However, the cathinone analogs found in abuse-ready 'bath salts' products are chemically distinct from both of these substances, although they can share either monoamine reuptake-inhibiting or monoamine-releasing mechanisms of action with the traditional psychostimulants. Nevertheless, a fundamental principle of pharmacology is that the chemical structure of a drug will determine its interaction with specific brain recognition sites, so it is entirely possible that the cathinone-analogs may bind to additional targets for which cocaine and METH lack relevant affinity. This has left researchers working with these novel cathinone analogs in the unusual position of having to determine whether their biological effects are related to their

interactions with monoamine transporters, or whether they are perhaps mediated by binding to other, unexpected receptor systems.

In light of the growing popularity of the drugs present in commercial 'bath salts' preparations, it has become critically important to re-evaluate our understanding of the relationship between psychostimulant abuse and HIV infection. Increasing evidence suggests that there is a strong abuse potential for substituted cathinones, comparable to that exhibited by cocaine and METH [41–43]. Furthermore, these 'bath salts' products are more accessible than cocaine and METH and can be purchased easily from the comfort of home through the Internet. To date, no formal studies have tested the hypothesis that the cathinone analogs would have psychostimulant-like potentiating effects on HIV infection, or that HIV infection would potentiate the abuse-related effects of these novel drugs. These studies are absolutely critical to perform as more and more young people are being exposed to these compounds without understanding any of the potential risks associated with their use.

Compliance with Ethics Guidelines

Conflict of Interest Brenda M. Gannon, Emily E. Reichard and William E. Fantegrossi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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