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# Interactions of HIV and drugs of abuse: the importance of glia, neural progenitors, and host genetic factors

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## Abstract

Considerable insight has been gained into the comorbid, interactive effects of HIV and drug abuse in the brain using experimental models. This review, which considers opiates, methamphetamine, and cocaine, emphasizes the importance of host genetics and glial plasticity in driving the pathogenic neuron remodeling underlying neuro-acquired immunodeficiency syndrome (neuroAIDS) and drug abuse comorbidity. Clinical findings are less concordant than experimental work, and the response of individuals to HIV and to drug abuse can vary tremendously. Host-genetic variability is important in determining viral tropism, neuropathogenesis, drug responses, and addictive behavior. However, genetic differences alone cannot account for individual variability in the brain "connectome". Environment and experience are critical determinants in the evolution of synaptic circuitry throughout life. Neurons and glia both exercise control over determinants of synaptic plasticity that are disrupted by HIV and drug abuse. Perivascular macrophages, microglia, and to a lesser extent astroglia can harbor the infection. Uninfected bystanders, especially astroglia, propagate and amplify inflammatory signals. Drug abuse by itself derails neuronal and glial function, and the outcome of chronic exposure is maladaptive plasticity. The negative consequences of coexposure to HIV and drug abuse are determined by numerous factors including genetics, sex, age, and multidrug exposure. Glia and some neurons are generated throughout life and their progenitors appear to be targets of HIV and opiates/psychostimulants. The chronic nature of HIV and drug abuse appears to result in sustained alterations in the maturation and fate of neural progenitors, which may affect the balance of glial populations within multiple brain regions.

### Keywords

drug/substance abuse; gene polymorphisms; methamphetamine; cocaine; neurogenesis/gliogenesis; neuropathology; μ opioid receptor (*OPRM1*); chemokine (C-C motif) receptor 5 (*CCR5*); neuroimmunology; neuropharmacology

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# 1. INTRODUCTION

For several decades drug abuse has been recognized as a significant risk factor for acquiring HIV infection and has been suggested to worsen some aspects of HIV infection within the brain. However, the enormity of the problem has been emphasized by a sustained nearly two-decade effort of the National Institute on Drug Abuse (NIDA) to study and treat this problem. As initially affirmed by Dr. Alan I. Leshner, former director of NIDA, "Drug abuse and HIV are truly interlinked epidemics" (Swan, 1997; Biber, Neumann, Inoue, & Boddeke, 2007; Andres et al., 2011). Despite widespread acceptance of this concept and impressive new gains in our understanding of this problem, there is a realization that the interplay between HIV and drug abuse is more complex than initially surmised. Many authoritative reviews describing the effects of drug abuse on neuroAIDS have been published and our goal here is not to repeat past dialogue. During the past decade, there has been considerable new information—especially with respect to increasing evidence that glia are fundamental sites of convergent drug abuse-HIV interactions and the emerging realization of the influence of host genetic factors on the severity of drug abuse and neuroAIDS comorbid interactions. This review will highlight recent findings emphasizing the role of glia and genetic factors in shaping the interactions of opiates and psychostimulants with neuroAIDS. Reviews on the effects of cannabinoids and ethanol on HIV neuropathogenesis are provided elsewhere within this issue, and not repeated here.

## 1.1. OPIATES AND HIV—PRECLINICAL AND CLINICAL FINDINGS

In this review, we will use the term "opiate" to refer to products or derivatives that can be found naturally in the opium poppy, *Papaver somniferum*. Opiates include heroin, morphine, and codeine; whereas, "opioids" refer to the endogenous system of related peptides and receptors initially revealed through the actions of opiate drugs.

Chronic opiate abuse alone is sufficient to promote neurodegenerative changes in the CNS. Clinical evidence from a cohort of preferential opiate abusers in Edinburgh, UK demonstrates that chronic abuse accelerates Alzheimer's disease-like pathology in HIV-negative individuals (Ramage et al., 2005; Anthony et al., 2010). Chronic preferential opiate abuse caused an accumulation of hyperphosphorylated tau-positive neuropil threads in the frontal and temporal cortex, and in the locus coeruleus compared to similarly aged-control subjects (Anthony et al., 2010). Increases in hyperphosphorylated tau were accompanied by increases in glycogen synthase kinase 3β and cyclin-dependent kinase-5 levels, as well as microgliosis—indicative of accelerated aging, and signaling events associated with Alzheimer's disease prematurely (Anthony et al., 2010).

There are compelling reasons to investigate opioid and HIV interactions and their role in a more severe and/or accelerated neuropathogenesis. In a seminal pre-combination antiretroviral (cART) era investigation, the presence of multinucleated giant cells and HIV p24 reactivity in the CNS was found more frequently in preferential opioid drug users (25 of 45; 56 percent) than in non-drug-abusing men (6 of 35; 17 percent) with AIDS (Bell, Brettle, Chiswick, & Simmonds, 1998). Chronic opiate exposure has been reported to increase the progression to HIV encephalitis (HIVE) in pre-cART era reports (Bell et al., 1998; Nath et al., 2000; Bell et al., 2002), and also worsens neuropathology in cART-treated patients

(Smith, Simmonds, & Bell, 2014). Even in cART-treated patients, chronic opiates aggravate CNS inflammation (Anthony, Ramage, Carnie, Simmonds, & Bell, 2005; Anthony, Arango, Stephens, Simmonds, & Bell, 2008) and worsen HIV-associated neurocognitive disorders (HAND) symptomatology—including deficits in verbal and working memory and increased peripheral neuropathy (Cohen, 2009; Byrd et al., 2011; Byrd, Murray, Safdieh, & Morgello, 2012; Robinson-Papp et al., 2012; Meyer et al., 2013). A recent study of a cART naïve population of injecting drug users who preferentially abuse heroin in Indonesia showed consistent reductions in CD4 counts to non-injecting drug abusers (Meijerink et al., 2014). Another recent report suggests that concurrent exposure can selectively increase the severity some features of HIVE (Smith et al., 2014). Despite increasing clinical evidence that chronic opiate exposure can worsen neuroAIDS, it remains unknown how opioids interact with individual HIV expressed gene products to affect subclasses of neurons, astroglia, and microglia (Nath et al., 2002; Hauser, Fitting, Dever, Podhaizer, & Knapp, 2012).

Some clinical studies are inconsistent with the findings cited above, and report minimal or no neurocognitive differences between HIV ± opiate abuse (Royal, III et al., 1991; Donahoe & Vlahov, 1998), suggesting that there are critical genetic (Kreek, Bart, Lilly, LaForge, & Nielsen, 2005; Proudnikov et al., 2012), pharmacokinetic (Eap, Buclin, & Baumann, 2002), pharmacodynamic, sex (Zubieta et al., 2002; Becker & Hu, 2008; Hahn et al., 2014), and/or possible age-dependent differences among opiate abusers that can influence outcomes (discussed later). Moreover, the timing of opioid co-exposure in relation to the onset of HIV infection or vice versa may have a marked influence on outcome (Fitting et al., 2012). It is hoped that advances in the understanding of disease mechanisms, experimental models, and methodology will reveal opiate-HIV interactions with increasing clarity.

Preclinical studies more regularly suggest that chronic opiate exposure plays a fundamental role in the pathogenesis of HIV in the CNS (Hauser et al., 2012). Briefly, morphine can exacerbate HIV-1 toxicity through separate actions in neurons (Gurwell et al., 2001; Hu, Sheng, Lokensgard, & Peterson, 2005; Bruce-Keller et al., 2008), including human neurons (Hu et al., 2005; Turchan-Cholewo et al., 2006) and in glia. Many of the harmful neurotoxic effects are mediated through μ opioid receptors (MOR) (Zou et al., 2011; Hauser et al., 2012) and differ depending on the CNS cell type involved. Glial targets can include μ opioid receptor-expressing astroglia (Hauser et al., 2007; Zou et al., 2011; Hauser et al., 2012; El-Hage et al., 2013), microglia (Turchan-Cholewo et al., 2008; Turchan-Cholewo et al., 2009; Zou et al., 2011; Suzuki et al., 2011; El-Hage et al., 2013; Sorrell & Hauser, 2014), oligodendroglia (Hauser et al., 2009; Hauser et al., 2012; Hahn et al., 2014), and glial precursors (Khurdayan et al., 2004; Buch et al., 2007; Hahn et al., 2010; Hahn, Podhaizer, Hauser, & Knapp, 2012). Details of opiates and HIV interactions in neurons and glia have been reviewed previously (Hauser et al., 2005b; Hauser et al., 2006; Hauser et al., 2007; Banerjee et al., 2011; Abt & Meucci, 2011; Hauser et al., 2012; Reddy, Pilakka-Kanthikeel, Saxena, Saiyed, & Nair, 2012; Festa & Meucci, 2012; Dutta & Roy, 2012).

### 1.2. PSYCHOSTIMULANTS AND HIV

Numerous authoritative reviews exist on the generalized effects of chronic psychostimulant (such as methamphetamine, MDMA) abuse on brain pathology (Cadet & Krasnova, 2009;

Buttner, 2011; Buch et al., 2012; Clark, Wiley, & Bradberry, 2013; Cadet, Bisagno, & Milroy, 2014; Halpin, Collins, & Yamamoto, 2014). Evidence suggests that psychostimulants can act directly on both neurons and glia to disrupt CNS function and promote the injury of vulnerable subpopulations of neurons in the CNS. The vulnerable subpopulations include dopaminergic, noradrenergic, and serotonergic neurons. Minimal attention has been given to stimulants besides methamphetamine, such as 3,4-methylenedioxymethamphetamine (MDMA or ecstasy), ketamine, or γ-hydroxybutyrate (GHB) (Colfax & Guzman, 2006), other than evidence that club drug use increases risky sexual behavior associated with increasing HIV transmission (Zuckerman & Boyer, 2012).

Chronic methamphetamine abuse and disruptions to dopaminergic function are especially deleterious with HIV-infected individuals (Nath et al., 2000; Theodore, Cass, Nath, & Maragos, 2007; Nath, 2010). Methamphetamine addiction results in marked structural pathology in the brain (Berman, O'Neill, Fears, Bartzokis, & London, 2008) and increases the probability of neuropsychological deficiencies in HIV-infected individuals (Rippeth et al., 2004). Many comprehensive reviews exist on the mechanisms underlying the neurotoxic effects of methamphetamine alone (Quinton & Yamamoto, 2006; Cadet, Krasnova, Jayanthi, & Lyles, 2007; Theodore et al., 2007; Ferris, Mactutus, & Booze, 2008; Berman et al., 2008; Krasnova & Cadet, 2009; Cadet & Krasnova, 2009; Nath, 2010; Kaushal & Matsumoto, 2011; Coller & Hutchinson, 2012; Cisneros & Ghorpade, 2012; Clark et al., 2013; Cadet et al., 2014).. Briefly, methamphetamine has both direct and indirect toxic effects on neurons. Indirect neurotoxicity is mediated by disrupting glia and/or targets such as the blood brain barrier (BBB) or the immune system. Chronic methamphetamine exposure can be accompanied by neurodegeneration. Dopaminergic neurons and presynaptic terminals are particularly vulnerable (Czub et al., 2001; Flora et al., 2003; Theodore, Cass, & Maragos, 2006a).

Methamphetamine selectively injures neurons in specific brain regions such as the basal ganglia (Seiden & Ricaurte, 1987), although the precise sequence of direct and indirect events leading to neuronal injury is not fully understood. Acute exposure to methamphetamine induces rapid release of dopamine from presynaptic terminals, while chronic dopamine use results in lasting decreases in striatal dopamine and serotonin and their metabolites (Kogan, Nichols, & Gibb, 1976; Wagner et al., 1980; Cass, 1997) that are accompanied by the destruction of dopaminergic presynaptic terminals in the caudate nucleus (Wagner et al., 1980; Brunswick, Benmansour, Tejani-Butt, & Hauptmann, 1992; Nakayama, Koyama, & Yamashita, 1993; Krasnova & Cadet, 2009; Pereira et al., 2012; Halpin et al., 2014; Nickell, Siripurapu, Vartak, Crooks, & Dwoskin, 2014). Methamphetamine inhibits the function of the vesicular monoamine transporter 2 (VMAT2) (Hanson, Sandoval, Riddle, & Fleckenstein, 2004; Hanson, Rau, & Fleckenstein, 2004) and the dopamine transporter (DAT) (Volkow et al., 2001; Theodore, Cass, & Maragos, 2006b; Krasnova & Cadet, 2009; Cadet & Krasnova, 2009; Halpin et al., 2014; Nickell et al., 2014). VMAT2 transports dopamine (and other monoamines) from the cytosol into presynaptic vesicles (Qi, Miller, & Voit, 2008; Cartier et al., 2010), while DAT reuptakes dopamine from the synaptic cleft into the presynaptic terminal. A transmembrane pH gradient is necessary for vesicular uptake (Sulzer & Rayport, 1990). Methamphetamine, a weak base, limits acidification of the presynaptic cytoplasm and therefore can disrupt vesicular

transport. By targeting VMAT2, methamphetamine elevates levels of dopamine within the presynaptic terminal. Cumulative increases in dopamine and oxidative byproducts further reduce levels of VMAT2 creating a destructive positive feedback cycle. In humans, many (but not all) markers of dopamine nerve terminals, such as dopamine itself, tyrosine hydroxylase, and DAT, are decreased in brains of psychostimulant abusers (Wilson & Kish, 1996; Wilson et al., 1996). These effects may be enduring (McCann et al., 1998).

Methamphetamine-related disruption of intracellular redox potential, nitrogen metabolism, and pH exert the greatest burden on vesicular trafficking at presynaptic terminals, which include losses in DAT (Fleckenstein, Metzger, Wilkins, Gibb, & Hanson, 1997; Brown et al., 2002; Hanson et al., 2004) and VMAT2 function (Miller, Gainetdinov, Levey, & Caron, 1999; Larsen, Fon, Hastings, Edwards, & Sulzer, 2002). The selective presynaptic harm may be worsened by excessive peripheral ammonia caused by concurrent methamphetamine-induced hepatotoxicity (Halpin & Yamamoto, 2012).

Dopamine and the accumulation of other amines within the presynaptic cytoplasm can activate trace amine-associated receptor 1 (TAAR1) (Borowsky et al., 2001; Bunzow et al., 2001; Reese, Bunzow, Arttamangkul, Sonders, & Grandy, 2007). TAAR1 is localized within the presynaptic membranes of monoaminergic neurons and located intracellularly suggesting segregation to internalized vesicles (Xie & Miller, 2009; Revel et al., 2011). TAAR1 reportedly can dimerize with dopamine D2 receptors (Espinoza et al., 2011) and TAAR1 activation phosphorylates DAT, resulting in increased dopamine efflux and eventually DAT internalization (Miller, 2011). TAAR1 likely mediates key aspects of aberrant function following methamphetamine (Xie & Miller, 2009) and perhaps cocaine (Revel et al., 2011) exposure.

Methamphetamine and cocaine exposure can result in excessive glutamate within the extracellular space (ECS) at synaptic and extrasynaptic sites (Miyatake, Narita, Shibasaki, Nakamura, & Suzuki, 2005; Quinton & Yamamoto, 2006; Davidson et al., 2007; Cadet et al., 2007; Kaushal & Matsumoto, 2011; Pereira et al., 2012). Glutamate overflow, especially at extrasynaptic sites (Sattler, Xiong, Lu, MacDonald, & Tymianski, 2000; Hardingham, Fukunaga, & Bading, 2002), can induce excitotoxic neuronal injury and even death through overactivation of extrasynaptic GluN2B NMDA receptors (Ivanov et al., 2006; Liu et al., 2007). The NMDA receptor antagonists MK-801 or dextromethorphan can attenuate methamphetamine neurotoxicity (Thomas & Kuhn, 2005), suggesting that microglial activation and dopamine terminal losses may be intimately linked to excitotoxic glutamatergic transmission and imbalances in synaptic and extrasynaptic glutamate (Beardsley & Hauser, 2014).

Chronic HIV-1 or SIV infection deplete dopamine and reduce the number of dopamine terminals in the basal ganglia (Reyes, Faraldi, Senseng, Flowers, & Fariello, 1991; Nath et al., 2000; Czub et al., 2001; Maragos et al., 2002; Wang et al., 2004), which appears to be worsened by methamphetamine exposure (Nath et al., 2000; Czub et al., 2001; Maragos et al., 2002; Cass, Harned, Peters, Nath, & Maragos, 2003; Scheller et al., 2005) or dopamine agonists (Nath, Maragos, Avison, Schmitt, & Berger, 2001; Czub et al., 2001; Czub et al., 2004).

Dopaminergic neurons are especially vulnerable to Tat and/or gp120-induced insults (Hu, Sheng, Lokensgard, Peterson, & Rock, 2009). When methamphetamine is administered after intrastriatal HIV-1 Tat injection, it acts synergistically to diminish levels of dopamine and dopamine metabolites (Maragos et al., 2002). Dopamine D2 receptors levels are also decreased as indicated by reductions in raclopride binding (Maragos et al., 2002). Interestingly, HIV-1 Tat may directly inhibit VMAT2 function in the CNS (Theodore, Cass, Dwoskin, & Maragos, 2012). More recently, HIV-1 Tat has been demonstrated to interact directly with the DAT (Zhu, Mactutus, Wallace, & Booze, 2009; Zhu, Ananthan, Mactutus, & Booze, 2011; Midde, Gomez, & Zhu, 2012; Midde et al., 2013). Thus, HIV-1 Tat disrupts the same molecular targets as methamphetamine albeit through independent mechanisms, which is likely to contribute to the devastating neurological and psychiatric consequences of methamphetamine and HIV comorbidity.

Brain aging has been demonstrated to be accelerated in cocaine abusers (Ersche, Jones, Williams, Robbins, & Bullmore, 2013). Since psychostimulants alone cause marked pathogenesis, it is not surprising that in combination with HIV, the pathologic consequences to the brain can be severe (Cadet et al., 2014). Many authoritative reviews exist on cocaine neurotoxicity (Ferris et al., 2008; Nath, 2010; Bowers, Chen, & Bonci, 2010; Narayanan, Mesangeau, Poupaert, & McCurdy, 2011; Kousik, Napier, & Carvey, 2012; Pierce & Wolf, 2013; Clark et al., 2013; Cadet et al., 2014). Accordingly, only some of the more recent findings regarding the actions of cocaine will be discussed.

The dopamine transporter is thought to be a major site of cocaine action. By inhibiting DAT function, dopamine accumulates in the synaptic cleft, overactivating dopamine receptors postsynaptically and increasing its rewarding properties. Restricting DAT function alone as demonstrated in DAT knockout mice, however, is insufficient to block cocaine conditioned-place preference (Sora et al., 1998). When dopamine and serotonin transporters are both deleted, mice no longer self-administer or show cocaine place preference (Sora et al., 2001). These findings and others suggest that dopamine and serotonin, as well as norepinephrine, act in concert to contribute to cocaine's addictive properties (Sora et al., 2001; Hall et al., 2004; Hall et al., 2009). Overall, cocaine appears to primarily act by inhibiting presynaptic dopamine transporters, but also hinders serotonin and norepinephrine transporters (Sora et al., 2001; Hall et al., 2004; Kreek et al., 2005; Hall et al., 2009), and may also secondarily dysregulate inhibitory GABAergic function (Cameron & Williams, 1994). Cocaine also modulates the endogenous opioid system, especially MOR, κ opioid receptors (KOR), and preprodynorphin (Kreek et al., 2005).

### 1.3. THE CENTRAL ROLE OF GLIA

Although neuronal interconnections form the synaptic circuitry that underlie behavior (Hebb, 1949; Yuste & Bonhoeffer, 2001), astroglia and microglia provide essential structural, trophic, and metabolic support necessary for maintaining synaptic integrity and function. Importantly, in HIV, glia are both targets and effectors in the progression of disease. Not only do glia harbor the virus and release inflammatory mediators, but they may also be functionally compromised and/or killed in the process. Unlike neurogenesis, which is restricted to limited brain regions and neuronal types, glia continue to be generated

throughout ontogeny (discussed below). This includes microglia, and all classes of macroglia (including astroglia, oligodendroglia, and ependymal cells). The ability of glial populations to respond in a dynamic fashion to both HIV infection/exposure and to drugs of abuse prompts our glia-centric viewpoint, which provides extensive insight into the pathogenesis of neuroAIDS and into the molecular and cellular mechanisms by which drug abuse affect the progression the disease.

## 2. MICROGLIA

In the central nervous system (CNS), the principal cell types that are productively infected are perivascular macrophages and brain-resident microglia. Astrocytes can also become infected, and this is particularly evident *in vitro*; however, the production of new virions by astrocytes is greatly restricted compared to microglia (discussed below). Although the virus itself can infect and replicate in microglia, much of the subsequent spiraling inflammation, synaptodendritic injury, and neurotoxicity arise from the response of bystander microglia and astroglia that are not necessarily infected.

### 2.1. MICROGLIA AS INNATE IMMUNE EFFECTORS

A seminal study by Ginhoux et al., (2010) reports that microglia originate from a mesenchymal (incipient myeloid) precursor in the murine yolk sac on embryonic day 8.25–8.5, seed the incipient CNS in embryonic day 9.25–9.5, and remain in the CNS throughout life. Despite considerable overlap with myeloid-lineage cells (“myeloid” refers to the bone marrow) such as monocytes and macrophages, which also originate from a common progenitor in the yolk sac, microglia are an ontogenically distinct population—since they never inhabit the bone marrow (Saijo & Glass, 2011). This finding concurs with evidence that microglia and perivascular CNS macrophages can differ functionally and phenotypically—especially in their response to HIV (see below).

Akin to monocyte-derived macrophages (MDMs), microglia possess a wide variety of “pattern” or “pathogen” recognition receptors (PRRs) related to innate immune function. PRRs include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain receptors (NOD-like receptors or NLRs), Mac-1, CD14 (Nadeau & Rivest, 2000), and a wide-variety of scavenger receptors, including those that recognize and remove low-density lipoproteins (Husemann, Loike, Kodama, & Silverstein, 2001; Coraci et al., 2002), and receptors for advanced glycation end-products (RAGE) (Farina, Aloisi, & Meinl, 2007). Microglia can express major histocompatibility complex-I (MHC-I) and MHC-II complexes, that allow them to contribute to adaptive immunity by processing both intracellular and extracellular foreign proteins for presentation as antigens to T-lymphocytes.

### 2.2. MICROGLIA AND HIV

Despite substantial overlap, microglia and perivascular CNS macrophages can differ functionally and phenotypically in their response to HIV (Fischer-Smith et al., 2001; Guillemin & Brew, 2004) or simian immunodeficiency virus (SIV) (Williams et al., 2001). Given that microglia reside and replicate within the brain throughout life (Ginhoux et al., 2010; Saijo & Glass, 2011), the virus must enter the brain before microglia can become

infected. Perivascular macrophages are the major cell by which HIV (Fischer-Smith et al., 2001) or SIV (Williams et al., 2001) seeds the CNS. Perivascular macrophages originate from HIV infected and uninfected MDMs, which are thought to have some ability to traffic bidirectionally between the blood and perivascular sites within the CNS parenchyma (Gonzalez-Scarano & Martin-Garcia, 2005). Although infected MDMs are the major source of virions initially seeding CNS microglia, once the infection is established in microglia (Cosenza, Zhao, Si, & Lee, 2002)—current evidence suggests that resident microglia become a sustained site of both active and latent infection (Kaul, Garden, & Lipton, 2001; Garden, 2002; Persidsky & Gendelman, 2003; Fischer-Smith & Rappaport, 2005; Kramer-Hammerle, Rothenaigner, Wolff, Bell, & Brack-Werner, 2005; Gonzalez-Scarano & Martin-Garcia, 2005), and that HIV evolves independently in distinct CNS cell types (Schnell, Joseph, Spudich, Price, & Swanstrom, 2011). The exchange of HIV between MDMs and microglia makes the brain a reservoir of latent infection (Kaul et al., 2001; Persidsky & Gendelman, 2003; Fischer-Smith & Rappaport, 2005; Kramer-Hammerle et al., 2005; Gonzalez-Scarano & Martin-Garcia, 2005; Schnell et al., 2011; Joseph et al., 2014). This is thought to be particularly important in the post-cART era in which antiretroviral drugs have more limited access to the CNS parenchyma (where microglia reside) because of the BBB.

Infected macrophages and microglia produce “virotoxins” (Nath & Geiger, 1998), i.e., viral protein products such as Tat and gp120, Vpr and others, as well as “cellular toxins” including extracellular reactive oxygen species (ROS), reactive nitrogen species (RNS), and numerous cytokines, including TNF-α, IL-1β, IFN-γ, and IL-6, and chemokines (Persidsky, Buttini, Limoges, Bock, & Gendelman, 1997; Seilhean et al., 1997; Fiala et al., 1997; Kraft-Terry, Buch, Fox, & Gendelman, 2009). Both virotoxins and cellular toxins can independently interact in unique ways with opiates and psychostimulants, and will be the topic of the discussions that follow. In addition, cellular toxins [e.g., quinolinic acid (Guillemin, Kerr, & Brew, 2005) or the neurotoxic amine, Ntox (Giulian et al., 1996)], as well as excess glutamate (Gupta et al., 2010), released by macrophages/microglia also have toxic bystander effects on neighboring neurons (Mayne, Holden, Nath, & Geiger, 2000; Langford & Masliah, 2001; Saha & Pahan, 2003; Schuenke & Gelman, 2003; Yi, Lee, Liu, Freedman, & Collman, 2004; Eugenin et al., 2006; Alirezaei, Kiosses, Flynn, Brady, & Fox, 2008; Turchan-Cholewo et al., 2009; Kiebala & Maggirwar, 2011). The actions of macrophages and microglia in the context of HIV have been extensively reviewed (Masliah et al., 1997; Kaul et al., 2001; Gonzalez-Scarano & Martin-Garcia, 2005).

Microglia can express a wide-variety of neurotransmitter receptors, including AMPA and NMDA receptors, which presumably allows microglia to coordinate and synchronize their responses with neuronal function (Hanisch & Kettenmann, 2007; Pocock & Kettenmann, 2007; Gras et al., 2012; Eggen, Raj, Hanisch, & Boddeke, 2013; Prada, Furlan, Matteoli, & Verderio, 2013). Excitotoxic levels of glutamate can trigger inflammatory responses by microglia, including the release of proinflammatory cytokines and reactive oxygen species (ROS) (Noda, Nakanishi, Nabekura, & Akaike, 2000; Hagino et al., 2004). HIV-1 virions and gp120 have been shown to increase levels of extracellular glutamate by direct effects on uptake mechanisms in astroglia (Wang et al., 2003), and the increased glutamate likely drives further microglial reactivity.

**2.2.1. Opioid and HIV actions in microglia—**Microglia display more pronounced glial reactivity than astroglia in HIV-infected opiate abusers (Anderson et al., 2003). HIV-1 gp120 and/or Tat released from infected glia (microglia and astrocytes) trigger (1) cytokine release, (2) inflammatory lipid production by bystander glia (Bandaru, Patel, Ewaleifoh, & Haughey, 2011), (3) destabilize intracellular ion homeostasis, and (4) increase extracellular glutamate (Wang et al., 2003; Zou et al., 2011; Podhaizer et al., 2012) and extracellular ATP levels (Sorrell & Hauser, 2014) (figure 1). Bystander neurons are directly and indirectly damaged (Masliah et al., 1997; Kaul et al., 2001; Gonzalez-Scarano & Martin-Garcia, 2005; Mattson, Haughey, & Nath, 2005; Ellis, Langford, & Masliah, 2007). Opiates can affect all aspects of the above processes, including (1) MDM trafficking across the BBB, (2) viral replication in MDMs, microglia and astroglia (largely in *in vitro* studies), (3) the production of proinflammatory cytokines and chemokines, and (4) losses in extracellular ion homeostasis. The effects of opiates in MDMs and microglia have been comprehensively reviewed elsewhere (Chao, Hu, & Peterson, 1996; Rock & Peterson, 2006; Hauser et al., 2007; Banerjee et al., 2011; Hauser et al., 2012; Dutta & Roy, 2012; Regan, Dave, Datta, & Khalili, 2012; Reddy et al., 2012). Accordingly, only a few recent findings will be briefly considered in the present review.

Acute exposure to opiate drugs such as morphine (El-Hage et al., 2013) or methadone (Li et al., 2002) tend to increase HIV replication by infected microglia. However, depending on the duration and timing of exposure, morphine can increase, act in a neutral manner, or inhibit HIV expression (Peterson, Gekker, Hu, Cabral, & Lokensgard, 2004). Moreover, selective MOR agonists such as endomorphin-1, but not DAMGO or morphine (Peterson et al., 1999) can increase HIV-1 replication in infected microglia—suggesting the involvement of a non-traditional MOR variant in HIV replication (Peterson et al., 1999) or suggesting that “biased agonism” (Hauser et al., 2012) may be operative. We have recently found that specific subsets of MOR splice variants, including MOR-1X and MOR-1K were differentially expressed by human astrocytes, but not expressed at detectable levels in microglia (Dever, Xu, Fitting, Knapp, & Hauser, 2012; Dever et al., 2014). Moreover, the expression of each MOR variant may be differentially regulated by HIV and in a cell specific manner (Dever et al., 2012; Dever et al., 2014). Thus, microglia express a subset of MOR variants each of which may respond uniquely to morphine and/or HIV (Dever et al., 2012; Dever et al., 2014). Collectively, the findings indicate that the effects of MOR activation on HIV replication and the response of microglia to HIV (discussed below) are complex and may differ significantly depending on context.

Acute exposure of microglia to HIV-1 Tat increases glutamate release via the $x_c^-$ cystine-glutamate antiporter (Gupta et al., 2010). Tat-dependent increases in extracellular glutamate were attenuated by inhibitors of p38, p42/44 MAPK, or NADPH oxidase or by inhibiting the $x_c^-$ cystine-glutamate antiporter directly (Gupta et al., 2010). Interestingly, morphine co-exposure with Tat can significantly increase glutamate release from microglia above maximal levels of secretion seen with Tat alone (Gupta et al., 2010). Although excitatory amino acid transporters-1 and 2 (EAAT1 or GLAST and EAAT2 or GLT-1, respectively) are minimally expressed by resting microglia and thought to be primarily expressed by astrocytes, recent evidence suggests both transporters are inducible in microglia with

immune activation (Gras et al., 2011). Because the function of EAAT1/2 is reduced markedly by morphine by itself (Zou et al., 2011), or in combination with Tat (Zou et al., 2011) or gp120 (Podhaizer et al., 2012) in astrocytes, future studies examining the potential contributions of microglial EAAT1/2 to HIV protein ± morphine-induced increases in extracellular glutamate are warranted.

Chronic opiates disrupt glial function, which is especially problematic in microglia where normal cellular functions have been hijacked by the virus (Hauser et al., 2012). HIV-1 alone causes increases in extracellular glutamate, ROS, and reactive nitrogen species (RNS) by overactivating microglia (Gendelman et al., 1997; Nath, 1999; Kaul et al., 2001; Kaul & Lipton, 2005; Gonzalez-Scarano & Martin-Garcia, 2005; Li, Li, Steiner, & Nath, 2009). Opiates have been shown to modulate (typically, but not always, worsening) all of these neuroinflammatory events (Chao et al., 1996; Rock & Peterson, 2006; Hauser et al., 2007; Banerjee et al., 2011; Hauser et al., 2012; Dutta & Roy, 2012; Regan et al., 2012; Reddy et al., 2012). However, the nature of opiate-HIV interactions in microglia is complicated and depends on a variety of factors that are incompletely understood. For example, we find that isolated microglia display transient increases in cytokine and ROS production in response to acute morphine and HIV-1 Tat co-exposure that are quite robust (Turchan-Cholewo et al., 2009). However, after 24 h of sustained exposure to morphine and Tat the inflammatory response of isolated microglia has faded to levels below that seen with Tat alone and this is not due to increased microglial death (Turchan-Cholewo et al., 2009). Alternatively, when microglia are cocultured with astroglia (Zou et al., 2011; Podhaizer et al., 2012; Hauser et al., 2012), or when glial inflammation and/or neuronal injury is examined *in vivo* (Bruce-Keller et al., 2008; El-Hage, Bruce-Keller, Knapp, & Hauser, 2008; Fitting et al., 2010a), prolonged morphine and HIV-1 Tat co-exposure results in neuroinflammation and/or neuronal injury that is evident for as long as 10 days. Although the sustained microglial activation is presumed to be driven through reverberating inflammatory signaling between MOR-expressing astroglia and microglia (Suzuki et al., 2011; Zou et al., 2011; Podhaizer et al., 2012; Hauser et al., 2012), additional study is needed to confirm this notion and to identify the mechanisms involved.

MDMs can display phenotypic heterogeneity in their expression of PRRs and in response to regional differences in the extracellular milieu (Kigerl et al., 2009). CD163 and CD16 co-expressing MDMs appear to be preferentially involved in HIV (Ancuta, Wang, & Gabuzda, 2006; Fischer-Smith, Tedaldi, & Rappaport, 2008) or SIV (Borda et al., 2008) replication and AIDS progression. Akin to MDMs, microglia can also display considerable functional heterogeneity (Carson et al., 2007; Hanisch & Kettenmann, 2007; Saijo & Glass, 2011; Scheffel et al., 2012; Hanisch, 2013), and a variety of intermediate states of activation (Colton, 2009). The phenotypic heterogeneity extends to opioid receptors and endogenous opioid peptides, since both macrophages and microglia can variably express MOR, δ, and κ opioid receptors (Chao et al., 1996; Peterson, Molitor, & Chao, 1998; Sheng, Hu, Lokensgard, & Peterson, 2003; Gekker et al., 2004; Turchan-Cholewo et al., 2008).

Emerging evidence indicates that microglia contribute to synaptic plasticity and the stability of synaptodendritic structure during maturation and in response to CNS disorders in adults (Wake, Moorhouse, Jinno, Kohsaka, & Nabekura, 2009; Tremblay, Lowery, & Majewska,

2010; Paolicelli et al., 2011; Ransohoff & Stevens, 2011; Antonucci et al., 2012). Opiate drugs such as morphine and methadone can directly trigger the retraction of dendritic spines in cerebral cortical neurons (Liao, Lin, Law, & Loh, 2005; Liao et al., 2007; Liao, Grigoriants, Loh, & Law, 2007), and affect the plasticity of adult neurons (Robinson & Kolb, 1999; Robinson & Kolb, 2004; Liao et al., 2005; Liao et al., 2007; Liao et al., 2007). Morphine's actions at MOR trigger decreases in NeuroD phosphorylation that impede glutamatergic signals originating from AMPA receptors (Liao et al., 2005). Subsequent increases in MOR-driven, dynamin-dependent receptor internalization retracts spines (Liao et al., 2005; Liao et al., 2007; Liao et al., 2007). In striatal medium spiny neurons, the relationship is less clear since only a subset of medium spiny neurons express MOR, despite evidence indicating that opiate-induced spine losses are consistent among all medium spiny neurons (Fitting et al., 2010a). While morphine may disrupt the excitotoxic response by decreasing NeuroD phosphorylation, and restricting glutamatergic transmission through neuroprotective AMPA and NMDA receptor subtypes (Liao et al., 2005; Liao et al., 2007; Liao et al., 2007), neurons in the striatum are less likely to be directly affected than in the cerebral cortex since only a subset of medium spiny neurons express MOR. MOR-expressing microglia and astroglia appear to contribute to the interactive neurotoxicity of morphine and Tat in the striatum (Zou et al., 2011; Sorrell & Hauser, 2014). In addition, e.g., GABA and fractalkine may serve as "off" signals—switching off overactive microglia (Beardsley & Hauser, 2014), and opiates can possibly modify these signals (Krebs, Gauchy, Desban, Glowinski, & Kemel, 1994; You et al., 1996; Steiner & Gerfen, 1998; McQuiston, 2007; Bagley et al., 2011; Suzuki et al., 2011). Thus, the innate immune and neurotransmitter signals disrupted by opiates and HIV strategically converge and are integrated into a unique "neuroimmune" logic by microglia.

### 2.2.2. Psychostimulant and HIV actions in microglia

**2.2.2.1. Methamphetamine and HIV:** Methamphetamine enhances HIV-1 replication in microglia (Liang et al., 2008). In addition to direct effects on viral replication, combined HIV Tat or gp120 and methamphetamine induce oxidative stress and free radical production in the CNS, which likely originates from reactive microglia (Banerjee, Zhang, Manda, Banks, & Ercal, 2010).

Psychostimulants including methamphetamine, cocaine, and ecstasy have all been suggested to activate the innate immune system (Clark, Wiley, & Bradberry, 2013). Immune activation may be an essential component of neurobiological adaption in alcohol and cocaine addiction (Crews, Zou, & Qin, 2011). Neuronal damage-associated molecular patterns (DAMPs), can directly activate, or under pathophysiological conditions, overactivate microglia (Block, Zecca, & Hong, 2007; Biber et al., 2007). DAMPs are released from stressed or injured cells (Bianchi, 2007; Srikrishna & Freeze, 2009) and trigger innate immune activation. Multiple classes of PRRs appear to be triggered through drug and alcohol abuse (Crews et al., 2011; Yakovleva, Bazov, Watanabe, Hauser, & Bakalkin, 2011; Beardsley & Hauser, 2014). Methamphetamine also reportedly affects subpopulations through the activation of trace aminoacid associated receptor-1 (TAAR1) (Bunzow et al., 2001; Reese et al., 2007; Xie & Miller, 2009). TAAR1 is co-expressed on dopamine D2 receptor and DAT-positive neurons

in the striatum and TAAR1 activation results in increases in cAMP levels (Xie & Miller, 2009; Espinoza et al., 2011).

Alternatively, dopamine and norepinephrine, which accumulate in the synaptic cleft following psychostimulant exposure, are thought to be able to elicit responses in microglia (Farber, Pannasch, & Kettenmann, 2005), while $GABA_B$ receptor activation reduces lipopolysaccharide (LPS) –induced IL-6 and IL-12 p40 release (Kuhn et al., 2004). Minocycline preferentially blocks macrophage/microglial activation (IL-1β and IL-6 are attenuated, but not TNF-α), but fails to mitigate striatal dopaminergic neurotoxicity because minocycline does not attenuate methamphetamine-induced increases in TNF-α (Sriram, Miller, & O'Callaghan, 2006). Thus, as noted earlier in the context of opiate abuse, the innate immune and neurotransmitter signals disrupted by psychostimulants converge in microglia, which attempts to integrate the diverse input into a coordinated and measured response.

HIV-1 activates microglia directly causing increases in both viral and cellular toxins as outlined earlier. Tat alone mediates much of the glial proliferative and cytokine/chemokine-secreting effects of HIV-1. Methamphetamine exacerbates the neurotoxic effects of HIV-1 through enhanced cytokine production and microglial activation (Theodore et al., 2006a; Theodore et al., 2006b; Theodore et al., 2007) (Figure 2). Dopamine losses evident in the SIV model can be prevented by inhibiting macrophage/microglial activity (Scheller et al., 2005). As with methamphetamine, HIV-1 Tat causes a rapid increase in cortical neuronal excitability that is exacerbated by cocaine (Napier, Chen, Kashanchi, & Hu, 2014). However, in the case of cocaine, despite considerable overlap, some of the events triggering neuroinflammation and microglial activation differ. For example, TAAR1 is activated by methamphetamine and MDMA, but may play a less central role in cocaine's actions (Bunzow et al., 2001).

Considerable evidence points toward sigma-1 receptors as a molecular target of cocaine actions (Su, Hayashi, Maurice, Buch, & Ruoho, 2010; Matsumoto, Nguyen, Kaushal, & Robson, 2014). Sigma-1 receptors are widely expressed throughout cells of the nervous system and elsewhere, and can contribute to a variety of pathological processes (Maurice & Su, 2009; Su et al., 2010). Cocaine increases chemokine (C-C motif) receptor 5 (CCR5) and CXCR4 HIV co-receptor expression, while transiently viral replication in human PBMCs in vitro (Roth, Whittaker, Choi, Tashkin, & Baldwin, 2005). Cocaine significantly increases the number of HIV-infected human peripheral blood mononuclear cells (PBMCs) and increases viral load in an infectious humanized SCID mouse model of HIV (Roth et al., 2005). In these studies, the sigma-1 receptor antagonist, BD1047, attenuated the effects of cocaine on HIV replication in HIV-infected humanized SCID mice, suggesting the sigma-1 receptor is a molecular target of cocaine's actions (Roth et al., 2005). Peterson and colleagues similarly demonstrated using BD1047 that sigma-1 receptor blockade prevented cocaine-induced HIV replication in microglia (Gekker et al., 2006). These investigators subsequently showed the TGF-β inhibitor, SB-431542 (Inman et al., 2002), or immunoneutralizing TGF-β1 antibodies, to be effective in negating the cocaine-induced increases in HIV-1 expression (Gekker et al., 2006). Cocaine treatment accelerates monocyte extravasation across the endothelium of the BBB through an MCP-1-dependent

mechanism that is initiated via sigma-1 receptors (Yao et al., 2010; Yao et al., 2011). Understanding the regulation of MCP-1 expression and functional role of sigma-1 receptors following cocaine exposure should provide novel insight into the basic mechanisms by which cocaine augments the severity of neuroAIDS (Yao et al., 2010).

## 3. ASTROGLIA

### 3.1. CRITICAL FUNCTIONS IN NEURONAL SUPPORT AND GLIOTRANSMISSION

Astrocytes form a close association with neurons and are strategically positioned to provide structural support, and to maintain metabolic, trophic, and functional processes including synaptic transmission that were previously thought to be regulated by neurons themselves (Parpura, Basarsky, Liu, Jeftinija, & Haydon, 1994; Araque, Parpura, Sanzgiri, & Haydon, 1999; Volterra & Meldolesi, 2005; Haydon & Carmignoto, 2006). Astrocytes also express nearly every class of neurotransmitter receptor, which permits them to coordinate their response precisely with neurons (Zhang & Barres, 2010; Beardsley & Hauser, 2014). The “tripartite synapse” refers to the intimate association between astrocytes and pre- and post-synaptic interconnections (Parpura et al., 1994; Araque et al., 1999; Perea, Navarrete, & Araque, 2009). Gliotransmission refers to the selective uptake and/or release of specific neurotransmitters by astroglia through vesicular (Montana, Malarkey, Verderio, Matteoli, & Parpura, 2006), extracellular membrane microvesicles (Verderio et al., 2012; Verderio, 2013), and/or nanotubes (Verderio, 2013). Gliotransmission significantly modulates neurotransmission (De Pittà et al., 2012; Tewari & Parpura, 2013).

In addition to modulating synaptic transmission, astrocytes regulate extrasynaptic transmission within the extracellular space (ECS) of the CNS (Sykova & Nicholson, 2008). This includes regulating “intersynaptic crosstalk” or the movement of excess neurotransmitters, including glutamate, between synapses, as well as the management of ion homeostasis (Vargova, Jendelova, Chvatal, & Sykova, 2001; Sykova, 2005) and of the movement of water within the ECS (Amiry-Moghaddam et al., 2003; King, Kozono, & Agre, 2004). The coordinated movement of ions and water within the ECS ultimately regulates tissue volume, including brain swelling during specific pathological conditions (Sykova, 2005; Anderova et al., 2011; Zamecnik et al., 2012). Aquaporin-4 (AQP-4) channels expressed largely by astrocytes are critical for regulating the volume of water within the ECS (Amiry-Moghaddam et al., 2003; King et al., 2004). Because HIV-induced deficits in astroglial glutamate and perhaps $K^+$ buffering capacity, as well as AQP-4 function, appear to be independently disrupted by HIV and substance abuse (Wang et al., 2003; Li et al., 2006; Berman et al., 2006; Knackstedt, Melendez, & Kalivas, 2010; Kalivas & Volkow, 2011; Zou et al., 2011; Hauser et al., 2012; Cisneros & Ghorpade, 2012; Podhaizer et al., 2012), extrasynaptic transmission within the ECS is likely to be highly compromised in HIV-infected substance abusers.

### 3.2. INNATE IMMUNE EFFECTORS

Astroglia are particularly adept at sensing metabolic instability in neurons and in the surrounding microenvironment. They are critical for interpreting and translating intercellular communication between neurons and microglia—especially during pathologic situations

(Maragakis & Rothstein, 2006; Molofsky et al., 2012; Verkhratsky, Rodriguez, & Parpura, 2013). Astrocytes can express a variety of PRRs categories against PAMPs and DAMPs, including TLRs, NODs, complement receptors [CR1, CR2, C3aR, C5aR (Gasque, Dean, McGreal, VanBeek, & Morgan, 2000)], mannose receptor (Liu et al., 2004), and RAGE (Husemann & Silverstein, 2001; Farina et al., 2007; Beardsley & Hauser, 2014). Thus, astroglia can act as transducers--both sensing neuronal injury and conveying information about neuron injury to microglia. Emerging evidence also suggests that astrocytes may express MHC-II following injury or stress (Jensen, Massie, & De Keyser, 2013).

### 3.3. ASTROGLIA AND HIV

Astroglia (Gorry, Purcell, Howard, & McPhee, 1998; Brack-Werner, 1999; Gorry et al., 2003; Kramer-Hammerle et al., 2005; Kramer-Hammerle, Hahn, Brack-Werner, & Werner, 2005) and perhaps also pericytes (Nakagawa, Castro, & Toborek, 2012), are the only resident CNS cells besides microglia that can become infected. Unlike microglia, astroglia tend not to display productive infection; rather, they harbor latent infection that can be reactivated from latency by specific proinflammatory cytokines such as TNF-α, GM-CSF or IFN-γ in $SIV_{mac251}$-infected astrocytes (Guillemin et al., 2000; Carroll-Anzinger, Kumar, Adarichev, Kashanchi, & Al-Harthi, 2007; Narasipura et al., 2012) or specific, class I histone deacetylase (HDAC) inhibitors (Narasipura, Kim, & Al-Harthi, 2014). Latent HIV is dormant, meaning that viral DNA has been integrated into the host DNA, but that new virions are not being produced. A number of hypotheses have been put forth in an attempt to explain fundamental differences in the regulation of HIV infectivity by astroglia. The activation of NF-κB was proposed to play a less central role in driving viral production by astrocytes than in microglia (Conant, Atwood, Traub, Tornatore, & Major, 1994). Subsequent studies also suggested differences in Rev-astroglial RNA helicase DDX1 interactions (Fang et al., 2005). In addition, a specific class I HDACs and a lysine-specific histone methyltransferase, SU(VAR)3–9, demonstrated in an U87MG astroglial cell line (Narasipura et al., 2014), were proposed as uniquely restricting HIV transcription in astroglia. Overexpression of *nef* (an early, regulatory gene), but not *gag* (a late structural gene), is seen in approximately 20% of astrocytes in infected individuals (Saito et al., 1994). Accordingly, Nef serves as a marker and perhaps contributing factor of restricted HIV infection in astroglia (Saito et al., 1994).

Besides being cellular sites of latent infection (Canki et al., 1997; Bencheikh, Bentsman, Sarkissian, Canki, & Volsky, 1999; Brack-Werner, 1999; Kramer-Hammerle et al., 2005), astroglia respond robustly following exposure to HIV proteins (Tat and gp120) or intact virions (Wang et al., 2003; Li, Bentsman, Potash, & Volsky, 2007) by releasing proinflammatory cytokines. Following exposure to viral products, astroglia release toxic and inflammatory cellular products (e.g., glutamate, ROS or cytokines such as TNF-α, IFN-γ, and IL-6) creating pathophysiological conditions that are detrimental for neurons (Genis et al., 1992; Bell, 1998; Nath, Conant, Chen, Scott, & Major, 1999; Kaul et al., 2001; Garden, 2002; Persidsky & Gendelman, 2003).

The nature of the inflammatory response can differ among individual astrocytes (Zhang & Barres, 2010; Fitting et al., 2010b), as well as among microglia (Carson et al., 2007;

Scheffel et al., 2012; Hanisch, 2013). Astrocytes are quite heterogeneous in the expression of a wide variety of phenotypic characteristics (Emsley & Macklis, 2006), including many receptor classes, and/or in their response to cues within the local microenvironment of the CNS (Shao & McCarthy, 1994; Shao, Porter, & McCarthy, 1994; Zhang & Barres, 2010; Fitting et al., 2010b). Astroglial heterogeneity has been historically attributed to unique environmental milieu imparted by neighboring neurons. Conversely, astrocytes generated along specific spatiotemporal domains within the ventricular zone (VZ) retain unique phenotypic characteristics throughout life (Tsai et al., 2012). Domain-specific astroglial variants have recently been shown to specify synaptic identity and regulate the ability of neurons to regenerate (Tsai et al., 2012).

Opiates and psychostimulants destabilize astroglial function directly. The destabilization usurps the ability of astrocytes to support neurons metabolically and trophically, while disrupting gliotransmission. Despite some attempts at neuroprotection, the net consequences of exposing astroglia to opiates or psychostimulants is they are less likely to aid neurons or to mitigate a reactive microglial response to HIV infection (Hauser et al., 2007).

### 3.4. EFFECTS OF OPIATES AND HIV IN ASTROGLIA

Histopathological studies demonstrate that astrocytes display fewer reactive changes than microglia in a chronic opiate abusing cohort of HIV-infected patients (Anderson et al., 2003). Nevertheless, astroglial function is markedly affected and astroglia are able to transduce and amplify signals from HIV-infected or uninfected perivascular macrophages and microglia—even in the absence of substance abuse co-exposure (Hauser et al., 2007). The release of proinflammatory cytokines and chemokines (e.g., MCP-1, MCP-5, and RANTES) can recruit macrophages/microglia, and these newly arriving cells likely contribute to neurotoxicity (El-Hage et al., 2005). The consequences of opiate abuse and HIV interactions in astroglia have been exhaustively reviewed previously (Peterson et al., 1998; Hauser et al., 2005a; Hauser et al., 2007; Banerjee et al., 2011; Hauser et al., 2012; Dutta & Roy, 2012; Reddy et al., 2012). Accordingly, we will only highlight key aspects of the interactions in the paragraphs that follow.

The high degree of phenotypic heterogeneity and plasticity that occurs among individual astrocytes in the expression of HIV co-receptors (Podhaizer et al., 2012) or PRRs such as TLRs (El-Hage, Podhaizer, Sturgill, & Hauser, 2011), as well as in the response to HIV proteins Tat and gp120 (Fitting et al., 2010b) are often-overlooked. Moreover, the prevalence of HIV infection appears to increase in immature astroglia (Tornatore, Nath, Amemiya, & Major, 1991; Tornatore, Meyers, Atwood, Conant, & Major, 1994; Tornatore, Chandra, Berger, & Major, 1994; Messam & Major, 2000; Lawrence et al., 2004), suggesting developmentally regulated differences in susceptibility to HIV-1 by astrocytes. With respect to opioids, astrocytes can express MOR, δ (DOR), and κ opioid receptors (KOR) (Stiene-Martin & Hauser, 1991; Eriksson, Hansson, & Rönnbäck, 1992; Eriksson, Nilsson, Wagberg, Hansson, & Rönnbäck, 1993; Ruzicka et al., 1995; Gurwell et al., 1996; Hauser et al., 1996; Hauser & Mangoura, 1998; Stiene-Martin, Zhou, & Hauser, 1998; Stiene-Martin et al., 2001; Curtis, Faull, & Eriksson, 2007; Turchan-Cholewo et al., 2008). Moreover, astrocytes can express endogenous opioid peptides associated with the

preproenkephalin gene (Shinoda, Marini, Cosi, & Schwartz, 1989; Hauser, Osborne, Stiene-Martin, & Melner, 1990; Spruce, Curtis, Wilkin, & Glover, 1990) and preproenkephalin is upregulated by cytokines including IL-1β and interferon-γ (Low & Melner, 1990a; Low & Melner, 1990b; Ruzicka & Akil, 1997). Unlike neurons, which typically produce and release fully processed enkephalin pentapeptides with a high affinity for DOR, astroglia tend to release larger, intact or partially processed proenkephalin peptides that can have high affinity at DOR or KOR. Overall, the wide expression of MOR, DOR and KOR by astroglia makes them a significant target for both endogenous opioids and exogenous opiates.

By disrupting astrocyte function, opiate drug abuse likely subverts their ability to maintain a homeostatic balance of ions and neurochemicals within the ECS, which promotes neuronal injury and death. Morphine can modify cytokine and chemokine production by astroglia (Mahajan, Schwartz, Shanahan, Chawda, & Nair, 2002; El-Hage et al., 2005; Mahajan et al., 2005a; Mahajan et al., 2005b; El-Hage et al., 2008; Sawaya, Deshmane, Mukerjee, Fan, & Khalili, 2009; Avdoshina, Biggio, Palchik, Campbell, & Mocchetti, 2010). Opiates short-circuit the ability of astroglia to protect neurons from HIV (Hauser et al., 2005b; Hauser et al., 2007; reviewed in Hauser et al., 2012). Opiates can intrinsically affect the expression of the glutamate transporters GLAST (EAAT1) and GLT-1 (EAAT2) (Ozawa, Nakagawa, Shige, Minami, & Satoh, 2001; Mao, Sung, Ji, & Lim, 2002). In the presence of HIV-1 Tat, opiates exacerbate the deleterious effects of the disease on intracellular signaling and $[Ca^{2+}]_i$ homeostasis (El-Hage et al., 2005; El-Hage et al., 2008), which results in further reducing the ability to buffer extracellular glutamate (Zou et al., 2011). The failure to buffer extracellular glutamate lowers the threshold for excitotoxicity in neurons (Zou et al., 2011; Podhaizer et al., 2012). Furthermore, opiate exposure alone can increase ROS (Zou et al., 2011; Podhaizer et al., 2012) and some proinflammatory cytokines (Mahajan et al., 2002; Mahajan et al., 2005b) in sufficient amounts to potentially be directly neurotoxic (Zou et al., 2011).

HIV-1 Tat is a potent activator of NF-κB (Conant, Ma, Nath, & Major, 1996; El-Hage et al., 2008) resulting in the release of a large number of cytokines and chemokines by astroglia (Conant et al., 1998; Kutsch, Oh, Nath, & Benveniste, 2000; El-Hage et al., 2005; El-Hage et al., 2006b; El-Hage et al., 2008). Besides potential actions destabilizing glutamate and triggering inflammation, Tat shares a Cys-Cys-Phe motif found in β-chemokine sequences such as CCL5 (Albini et al., 1998) that at least partly account for Tat's chemotactic properties. HIV-1 Tat also destabilizes $Ca^{2+}$ in astroglia (El-Hage et al., 2005) by mechanisms involving $IP_3$-dependent release (Kumar, Manna, Dhawan, & Aggarwal, 1998). Increased $[Ca^{2+}]_i$ dysregulates nuclear-cytoplasmic trafficking of NF-κB subunits (El-Hage et al., 2008), and leads to release of CCL2, CCL5, IL-6 and TNF-α. Morphine exacerbates this cycle (El-Hage et al., 2005; El-Hage et al., 2006a; El-Hage et al., 2006b; El-Hage et al., 2008), presumably by augmenting Tat-induced increases $[Ca^{2+}]_i$. Unlike other neural cell types, MOR can couple to Gβγ (Bonacci et al., 2006; Mathews, Smrcka, & Bidlack, 2008), $G_{q/11}$-α (Hauser et al., 1996), and/or $G_s$α via MOR-1K splice variants (Dever et al., 2014) in astroglia resulting in cellular excitation. Opiate and HIV-induced increases in astroglial-derived cytokines in turn enhance microglial recruitment and activation (El-Hage et al., 2006b). Morphine's unique actions in HIV-1-exposed astrocytes, in particular, appear to drive escalating, intercellular feedback loops with microglia and perivascular macrophages

that increase and sustain inflammation (El-Hage et al., 2006b; Hauser et al., 2007). We have proposed that, unlike other HIV-1-infected organs, which also can harbor MOR-expressing macrophages, the brain is unique because of the inflated response of astroglia to opioids (Hauser et al., 2007; Hauser et al., 2012). As a partial test this assertion, we recently tested whether drugs with selective anti-inflammatory activity in glia could attenuate the deleterious effects of HIV and opiate exposure. We found that ibudilast (also known as AV411 or MN-166) or an analogue lacking phosphodiesterase activity (AV1013), both of which preferentially suppress glial inflammation, attenuates HIV-1 ± morphine-dependent increases in HIV-1 replication and in HIV-1 Tat ± morphine-induced cytokine release and neurotoxicity *in vitro* (El-Hage et al., 2014).

This concept is supported by findings that HIV Tat ± morphine-induced death of medium spiny neurons is largely mediated via MOR-expressing glia (Zou et al., 2011), including astroglia (El-Hage et al., 2005; El-Hage et al., 2006b; El-Hage et al., 2008) and microglia (Turchan-Cholewo et al., 2008; Bokhari et al., 2009; Turchan-Cholewo et al., 2009; Gupta et al., 2010). Alternatively, the extent to which synaptodendritic culling is similarly driven by glia has not yet been established. Although glia undoubtedly play a significant role, as noted earlier, there is some evidence that morphine can converge with HIV Tat to cause spine retraction through direct actions on the dendrites of cerebral cortical neurons (Liao et al., 2005; Liao et al., 2007; Liao et al., 2007). Additionally, since morphine can excite dopaminergic neurons projecting from the ventral tegmental area (VTA) to striatal neurons by hyperpolarizing inhibitory GABAergic interneurons in the VTA (Johnson & North, 1992), it is likely that HIV-1 and opiate-related alterations in synaptic organization are affected by a complex interplay of events.

### 3.5. Effects of psychostimulants and HIV in astroglia

A number of reviews on the effects of psychomotor stimulants by themselves (Cadet & Krasnova, 2009; Clark et al., 2013; Beardsley & Hauser, 2014; Cadet et al., 2014) and in the context of HIV (Hauser et al., 2007; Nath, 2010; Cisneros & Ghorpade, 2012; Buch et al., 2012) on astrocytes are available. Briefly, methamphetamine and cocaine are thought to affect astrocyte function through a variety of indirect and direct actions. The profile of inflammatory cytokines released by astrocytes in response to methamphetamine notably include the release of TNF-α, IL-1β, IL-6, and the chemokine MCP-1, as well as intercellular adhesion molecule-1 (ICAM-1) (Flora et al., 2002; Nakajima et al., 2004; Theodore et al., 2006a; Goncalves et al., 2008; Clark et al., 2013). The astroglial response to cocaine is more limited than the response to methamphetamine. Cocaine can increase the expression of TNF-α, IL-1β, and IL-6 transcripts, while downregulating the anti-inflammatory cytokine IL-10 (Clark et al., 2013). These cytokines fuel inflammatory cascades and the release of chemokines such as MCP-1, which recruit macrophages and activate microglia within the CNS (Yao et al., 2010). Glial inflammation is proposed to be an essential step in the maladaptive neuroplasticity accompanying addiction (Crews et al., 2011; Frank, Watkins, & Maier, 2011; Clark et al., 2013). Excessive or sustained high levels of inflammation result in neuronal injury and potentially neuronal death (Jayanthi et al., 2005; Krasnova & Cadet, 2009; Buttner, 2011).

Gliotransmission has been reported to be necessary for reinstatement of cocaine-seeking behavior (Turner, Ecke, Briand, Haydon, & Blendy, 2013). Mice expressing a dominant negative soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) variant driven by a GFAP-dependent promoter were used to selectively disrupt gliotransmission (Turner et al., 2013). However, in these studies, the transmitter substance(s) released during gliotransmission are uncertain. Gliotransmission can involve the vesicular release of excitatory transmitters, including glutamate, serine, and adenosine triphosphate (ATP) (Pascual et al., 2005; D'Ascenzo et al., 2007; Parpura & Zorec, 2010; Santello, Cali, & Bezzi, 2012; Martineau, 2013; Van Horn, Sild, & Ruthazer, 2013). Of these, glutamate appears to contribute to drug-seeking behavior and other aspects of cocaine addiction (Beardsley & Hauser, 2014)

In combination with methamphetamine, HIV Tat exacerbates the disruption of EAAT-2 and perhaps EAAT-1 (aka, glutamate/aspartate transporter or GLAST) in astroglia (Cisneros & Ghorpade, 2012), and may additionally increase the release of glutamate from injured presynaptic terminals. Interestingly, ceftriaxone, which upregulates EAAT2 expression in astroglia, protects neurons against Tat or gp120-induced injury (Rumbaugh, Li, Rothstein, & Nath, 2007). Collectively, methamphetamine and HIV appear to dysregulate the buffering of extracellular glutamate by astrocytes, which contributes to excitotoxic injury in neurons. Propentofylline, which is thought to affect multiple molecular targets in both astroglia and microglia (Sweitzer, Schubert, & De Leo, 2001; Sweitzer & De Leo, 2011), impairs reinstatement to cocaine through an EAAT-2-related mechanism (Reissner et al., 2014). Furthermore, anti-inflammatory drugs with preferential actions in glia such as minocycline and/or ibudilast can limit key aspects of methamphetamine's locomotor behaviors and/or reinforcing properties (Snider et al., 2012; Snider, Vunck, Hendrick, & Beardsley, 2012) or aspects of cocaine sensitization (Chen, Uz, & Manev, 2009; Chen & Manev, 2011).

Cocaine affects BBB permeability and increases MDM trafficking across the barrier (Fiala et al., 1998; Zhang et al., 1998; Gan et al., 1999). Key aspects of the higher rates of CNS infection (Fiala et al., 2005) and encephalitis (Clark et al., 2013) caused by cocaine are fueled by sigma 1 receptor-induced increases in MCP-1 derived from glia and especially astrocytes--recruiting new MDMs into the CNS (Yao et al., 2010). Moreover, sigma 1 receptor-dependent increases in the expression of activated-leukocyte cell adhesion molecule by endothelial cells (Yao et al., 2011), which increases diapedesis of MDMs and the recruitment of perivascular macrophages. Methamphetamine increases the shedding of matrix metalloproteinases (MMPs), especially MMP-1 and MMP-2 from astroglia, which can disrupt the blood brain barrier (BBB) (Conant et al., 2004). Besides, MMP-1 and MMP-2, HIV-1 Tat can increase MMP-5, which may reduce long-term potentiation (LTP) in the hippocampus (Conant et al., 2010). MMP-5 can cleave GluN1 NMDAR subunits (Szklarczyk et al., 2008) and aquaporin-4 (AQP-4).

AQP-4 expressed by astroglia (Rash, Yasumura, Hudson, Agre, & Nielsen, 1998) is essential for moving water from the ECS through astrocytes and across the BBB into the vasculature (King et al., 2004; Tait, Saadoun, Bell, & Papadopoulos, 2008). AQP-4 is intimately linked to astroglial function (King et al., 2004). AQP-4 levels are increased in HIV-associated dementia (HAD); however, it is uncertain whether this is a maladaptive or a

compensatory response to counteract the effects of chronic inflammation (St Hillaire et al., 2005). Interestingly, the effects of cocaine are attenuated in AQP-4-null mice, leading to speculation that AQP-4 regulates cocaine reinforcement and dependence by alternating dopamine and glutamate release associated with drug reward (Li et al., 2006). Although AQP-4 expression *per se* appears to be unaffected by cocaine exposure (Narayana et al., 2014), AQP-4-null mice display attenuated locomotor and reward responses to cocaine suggesting its involvement in the neurobiological actions of cocaine (Li et al., 2006). By virtue of their critical role in regulating the volume of water within the ECS (Amiry-Moghaddam et al., 2003; King et al., 2004), including pathological brain swelling (Sykova, 2005; Anderova et al., 2011; Zamecnik et al., 2012), AQP-4 channels are likely to be important in regulating HIV and psychostimulant interactions.

# 4. GENETIC FACTORS THAT MODULATE HIV-1 INFECTIVITY AND NEUROPATHOGENESIS

## 4.1. INTRODUCTION

There are huge differences in the susceptibility of individuals to addiction or to acquiring HIV.. Emerging evidence indicates that different gene polymorphisms underlie the marked differences in HIV infectivity and/or in the response to combination antiretroviral therapy (cART) among individuals. Gene profiling differences have also suggested that HAND disorders of different severity may represent fundamentally different disease courses, and not a continuum of a single pathophysiological process (Gelman et al., 2012).

Polymorphisms in the genes associated with HIV-1 co-receptors and/or their endogenous ligands can markedly influence AIDS progression (Smith et al., 1997; Winkler et al., 1998; Carrington, Dean, Martin, & O'Brien, 1999). CCR5 in particular (Carrington et al., 1999), and mutations thereof, e.g., CCR5Δ32 (Huang et al., 1996; Boven, van der Bruggen, van Asbeck, Marx, & Nottet, 1999), as well as mutations in key cytokines, e.g., IL-10 (Shin et al., 2000) or TNF-α (Quasney et al., 2001), or other genes linked to specific neurodegenerative disorders such as apolipoprotein ε4 (ApoE4) (Verghese, Castellano, & Holtzman, 2011) may have a marked influence on neuroAIDS outcome measures (Shapshak et al., 2004a; Shapshak et al., 2011). Mutations in other human gene products, such as the specific apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3G (APOBEC3G) (Kim et al., 2010), an innate viral restriction factor that inhibits the production of HIV (Mangeat et al., 2003; Shindo et al., 2003; Bishop, Holmes, Sheehy, & Malim, 2004), may have deleterious consequences. In this section, we will cite and discuss several examples in which human genetic variability is beginning to uncover essential sites of drug abuse and neuroAIDS interplay.

CCR5 plays a critical role in HIV infection as a co-receptor for entry of CCR5-preferring strains that appear largely responsible for initial infection (Berger, Murphy, & Farber, 1999; Moore, Kitchen, Pugach, & Zack, 2004). The importance of CCR5 in HIV infectivity is supported by evidence by a wide variety of approaches. CCR5 levels in general, and in brain MDMs and microglia, have been correlated with the severity of HIV neurologic disease (Vallat et al., 1998; An, Osuntokun, Groves, & Scaravilli, 2001). Individuals homozygous

for the CCR5Δ32 mutation resist infection by HIV (Huang et al., 1996; Boven et al., 1999). CCR5 blockade employing the antagonist maraviroc to inhibit viral entry has marked clinic efficacy (MacArthur & Novak, 2008). Experimental reductions in CCR5 levels using gene silencing strategies have been successful in reducing HIV infectivity experimentally (Lee et al., 1999; Anderson & Akkina, 2007).

The importance of HIV co-receptors in viral infectivity and pathogenesis cannot be underestimated. Polymorphisms of CCR5, such as CCR5Δ32 (Huang et al., 1996; Boven et al., 1999) or CCR2 (Smith et al., 1997), can confer significant protection against HIV progression, while other mutations can worsen disease progression. Two studies have demonstrated that dual single nucleotide polymorphisms (SNPs) in the RANTES gene promoter (−471 and −96) reduce HIV disease advancement (McDermott et al., 2000; Gonzalez et al., 2001), while only one of these studies found an effect on transmission risk (McDermott et al., 2000). The RANTES-28G mutation increases RANTES transcript levels and is associated with increased protection against the clinical progression of HIV infection (Liu et al., 1999). The apparent eradication of HIV in a patient receiving a transplant of hematopoietic stem cells harboring a mutation (CCR5Δ32) in the chemokine (C-C Motif) receptor 5 (CCR5), a major HIV co-receptor that facilitates cell infection with HIV, has highlighted the insights that might be gained into mechanisms of HIV infectivity/pathogenesis by studying the role of genetic variability (Hutter et al., 2009; Allers et al., 2011).

Although polymorphisms of CXCR4 also exist, these are far less frequently identified than CCR5 polymorphisms. A likely reason may be that the deletion of CXCR4 or its cognate ligand SDF-1/CXCL12 is lethal (Ma et al., 1998; Zou, Kottmann, Kuroda, Taniuchi, & Littman, 1998). Combined mutations in multiple HIV co-receptors and/or in the cognate ligands of these co-receptors can interact to confer more or less protection against HIV infectivity or subsequent pathogenesis (Shapshak et al., 2004b; Gelman et al., 2012; Levine, Sinsheimer, Bilder, Shapshak, & Singer, 2012). Lastly, “elite suppressors” or “controllers” is the term given a subset of individuals who maintain plasma HIV copy numbers below 50 copies/mL (Han et al., 2008). SNPs in macrophage inflammatory protein 1α coincide with differences in disease progression (Gonzalez et al., 2001). In sum, gene variations in β-chemokines and their receptors can have marked influences on the clinical course HIV infection. There is considerable debate regarding the extent to which combinations of protective/non-protective allelic variants contribute to the subset of patients who are elite suppressors and are able to intrinsically suppress HIV replication (Miura et al., 2008; Baker, Block, Rothchild, & Walker, 2009).

Levels of monocyte chemoattractant protein (MCP-1 or CCL2) and its cognate receptor, CCR2, are increased with HIV infection and coincide with neurological impairment (Sozzani et al., 1997; Cinque et al., 1998). MCP-1 is released by HIV-exposed MDMs, microglia, and astrocytes (Conant et al., 1998; Nath et al., 1999). MCP-1 released by resident glia has been proposed as a key event in recruiting MDMs into the brain, an event that is exacerbated by opiates and psychostimulants (Zhang et al., 1998; Fiala et al., 2005; Eugenin, Dyer, Calderon, & Berman, 2005; Eugenin et al., 2006; Hauser et al., 2007; Berman et al., 2008; Yao et al., 2010). MCP-1 release from glia, especially astroglia, is a

significant site of drug abuse and HIV interactions (Hauser et al., 2007). Morphine exacerbates the release of chemokines, especially RANTES and MCP-1, from HIV Tat-exposed astrocytes (El-Hage et al., 2005; El-Hage et al., 2006b) and microglia (Turchan-Cholewo et al., 2009) in a time- and concentration-dependent manner, while cocaine accelerates monocyte extravasation across the BBB endothelium through a MCP-1-dependent mechanism that is absent in CCR2 knockout mice (Yao et al., 2010). A number of mutations in the CCR2 and CCL2 genes have been demonstrated to affect aspects of HIV/AIDS. The CCR2 V64I allele is associated with a more rapid onset of neurocognitive impairment, but even after adjusting for estimated time of seroconversion, there is no correlation with increased viral loads in cerebrospinal fluid (CSF) or in plasma, of HIV-infected subjects (Singh et al., 2004). Interestingly, the CCR2 V64I allele affords some protection against progression to AIDS, especially during early phases of the disease process (Ioannidis et al., 2001; Mulherin et al., 2003), perhaps at the expense of CNS function. An MCP-1 (CCL2) -2578G/A promoter polymorphism was shown to enhance protein production and was associated with significantly reduced risk of acquiring HIV infection (Gonzalez et al., 2002). However, once infected, patients with this genotype showed faster disease progression and enhanced risk for HAD, presumably due to enhanced infiltration of infected monocytes (Gonzalez et al., 2002). CCR2 gene polymorphisms can act in a cooperative manner with other genes to affect HIV pathogenesis, including CCR5 (Rigato et al., 2008). By contrast, no connections were found between CCR2 V64I or CCR5Δ32 mutations and HIV infectivity in “preferential” opiate abusers in northeastern India (Sarkar et al., 2010). However, as is common with most drug abusing cohorts, complicated individual abuse patterns and polydrug use confound the interpretation of the findings: 59% of these subjects abused spasmo-proxyvon, which contains the synthetic opiates dextroprophoxyphene or prophoxyphene and acetaminophen (Mahanta, Borkakoty, Das, & Chelleng, 2009), 54% abused heroin, and 15% abused “brown sugar” (partially purified heroin) (Sarkar et al., 2010).

TNF-α is important in triggering subsequent proinflammatory cascades such that any abnormalities in the regulation of TNF-α responsiveness are likely to have resounding consequences for the CNS (Bradley, 2008; McCoy & Tansey, 2008). Accordingly, it is perhaps not surprising that polymorphisms in the TNF-α promoter are associated with higher incidence of HAND (Quasney et al., 2001). Notably, both classes of abused drugs, opiates and psychostimulants, can increase the release of TNF-α from HIV or virotoxin-exposed glia (Gendelman et al., 1997; Fiala et al., 1997; Zhang et al., 1998; Flora et al., 2002; Fiala et al., 2005; Sriram et al., 2006; Sawaya et al., 2009). Alternatively, it has been argued that while TNF-α appears to serve as a marker for HIV progression, interferon-γ may play a more central role as a causal factor in the development of the disease based on genetic analyses of polymorphisms of both genes in the same patient population (Shapshak et al., 2004a).

**4.1.1 Mitochondrial genetics—**Within the CHARTER cohort, several mtDNA SNP haplotypes are associated with marked protection from peripheral neuropathies (African haplogroup L1c and European haplogroup J) (Holzinger et al., 2012). mtDNA polymorphisms have also been linked to bipolar disorder, and may be associated with an

increased risk for neurodegenerative/neurocognitive disorders (Chinnery et al., 2001; Lin & Beal, 2006), especially those associated with aging (Kato, 2001). Dopaminergic neurons may be particularly susceptible to mtDNA damage (Bender et al., 2008). Interestingly, methamphetamine increases mtDNA damage (Bachmann et al., 2009), and CNS damage caused by *in utero* methamphetamine exposure can be rescued by increasing DNA repair through the enhancement of oxoguanine glycosylase 1 activity (Wong, McCallum, Jeng, & Wells, 2008).

### 4.2. GENE VARIATION IN OPIATE DRUG ABUSE AND HIV INTERACTIONS

Given the importance of host genetic variability in determining and revealing fundamental mechanisms underlying HIV infectivity and pathogenesis, might host genetics also reveal basic processes underlying the interactions between substance abuse and HIV? An examination of specific human gene polymorphisms, especially genes for drug receptors (Bond et al., 1998; Kreek, Nielsen, Butelman, & LaForge, 2005; Kreek et al., 2005; Kreek et al., 2012), enzymes affecting drug metabolism (Meyer & Zanger, 1997), and/or neurochemical systems thought to underlie addiction (Lachman et al., 1996; Nebert, McKinnon, & Puga, 1996; Li et al., 2004; Kreek et al., 2005; Levine et al., 2012), has identified significant correlative relationships between gene polymorphisms and substance abuse (Kreek et al., 2005; Yuferov, Levran, Proudnikov, Nielsen, & Kreek, 2010; Crystal et al., 2012; Manini, Jacobs, Vlahov, & Hurd, 2013; Jacobs, Murray, Byrd, Hurd, & Morgello, 2013). Because addiction is principally a CNS disorder with neurobehavioral/ neuropsychiatric underpinnings (Leshner, 1997; Volkow, Wang, Fowler, & Tomasi, 2012), examining substance abuse-HIV interactions in the brain seems a logical direction. The potential importance of studying human gene polymorphisms as an approach to identify novel factors and mechanisms underlying drug abuse and neuroAIDS pathogenesis cannot be underestimated.

In a sample population of 1,031 women, polymorphisms in *OPRM1*, the gene encoding MOR, were associated with the severity of HIV infection or the response to cART (Proudnikov et al., 2012). These investigators found both negative and positive correlations with HIV severity in a small subset of *OPRM1* polymorphisms, while most variants displayed no association with HIV progression. Interestingly, although a subset of the patients sampled undoubtedly were substance abusers, many were not—suggesting that MOR receptor is inextricably linked to processes influencing HIV pathogenesis irrespective of opiate exposure. Although the mode of action is unclear, MOR activation can alter the expression of HIV-1 chemokine coreceptors involved in HIV entry, and MOR can undergo heterologous desensitization with CXCR4 (Szabo et al., 2002; Steele, Henderson, & Rogers, 2003; Patel et al., 2006; Finley et al., 2008; Burbassi, Aloyo, Simansky, & Meucci, 2008; Pitcher et al., 2014) or CCR5 (Chen et al., 2004; Happel, Steele, Finley, Kutzler, & Rogers, 2008; Song et al., 2011). Lastly, non-opioid genes may influence opiate drug and HIV interactions. For example, the presence of an apolipoprotein ε4 (ApoE4) allele increases the likelihood of neurotoxicity in response to combined morphine and HIV-1 Tat exposure in isolated human neurons *in vitro* (Turchan-Cholewo et al., 2006). The mechanisms responsible for opiate interactions with ApoE4 are unclear. Possessing an ApoE4 allele and increased ApoE4 levels in CSF was associated with an increased probability of

neurocognitive impairment in HIV-infected patients in one study (Andres et al., 2011), while another failed to find a linkage between the ApoE4 gene frequency and cognitive deficits in HIV-infected subjects (Morgan et al., 2013).

A potentially important role of *OPRM1* splice variants in neuroAIDS is indicated by our findings showing quantitative differences in specific human MOR splice variant expression levels with HIV encephalitis and/or neurocognitive status (Dever et al., 2012; Dever et al., 2014). In addition, MOR-1 (exon 1), MOR-1A, MOR-1X, and MOR-1K splice variants appear to differ across CNS cell types (Dever et al., 2012; Dever et al., 2014). Evolving evidence suggests that there are significant functional differences among MOR splice variants (Pan et al., 2005; Majumdar et al., 2011; Dever et al., 2012; Xu et al., 2014; Lu, Xu, Xu, Pasternak, & Pan, 2014). Thus far, the findings are limited to neural cells isolated from a relative small number of individuals, and from imprecisely defined brain regions. However; if our initial findings remain supported, this would be highly significant—indicating the existence of quantitative and functional differences in MOR subtypes among cell types.

A novel, truncated 6-transmembrane spanning (6TM) MOR-1K splice variant has been described, which unlike canonical 7-transmembrane spanning (7TM) MOR isoforms, couples into $G_{\alpha}s$, increases $[Ca^{2+}]_i$ and nitric oxide, and causes cellular excitation (Shabalina et al., 2009; Gris et al., 2010). Interestingly, HIVE and perhaps cognitive impairment correlates with increased MOR-1K (Dever et al., 2014), but not with MOR-1A or MOR-1X splice variants (Dever et al., 2012), in patient samples obtained through the National NeuroAIDS Tissue Consortium.

Global RANTES/CCL5 knockout reduced microgliosis and was neuroprotective in mice concurrently treated with morphine and HIV-1 Tat protein (El-Hage et al., 2008). This insinuates that CCL5-to-CCR5 signaling increases neuroinflammation even in non-infectious models, suggesting that in addition to viral entry, CCR5 blockade may be inherently neuroprotective (El-Hage et al., 2008). Preclinical studies in the SIV model demonstrating maraviroc protection against inflammatory markers in neuroAIDS lend support to this assertion (Kelly et al., 2013). Moreover, findings from other investigators suggest that CCR5 blockade may have advantages in other aspects of disease management besides preventing viral entry (Hunt et al., 2013). CCR5 blockade, either genetically or by maraviroc, eliminates synergistic morphine and Tat-related neurotoxicity in glial-neuronal co-cultures (unpublished results).

The above findings and work of others demonstrating heterologous, bidirectional cross-desensitization (Steele et al., 2003; Rogers & Peterson, 2003; Chen, Geller, Rogers, & Adler, 2007; Happel et al., 2008; Song et al., 2011) or direct molecular interactions (Suzuki, Chuang, Yau, Doi, & Chuang, 2002; Chen et al., 2004) between CCR5 and MOR, are guiding the development of novel therapeutics that selectively target CCR5-MOR and HIV interactions. Using translationally relevant, infectious models, we have started to screen novel bivalent ligands comprised of linked CCR5 and opioid receptor antagonists, which selectively target putative CCR5-MOR heterodimers (Yuan et al., 2012; Yuan et al., 2013; El-Hage et al., 2013) (Figure 3).

## 5. NEURAL/GLIAL PROGENITORS AND HIV

Neural progenitor cells (NPCs) are the undifferentiated precursors of both neurons and macroglia (astroglia and oligodendroglia); infection of NPCs might either lead to (occasional reports of) viral expression in more differentiated derivatives, or might directly influence their development and/or survival. NPCs may also be targets of HIV through interactions with HIV-1 proteins, or through the influence of extracellular changes that occur as a consequence of microglial or astroglial infection (e.g. enhanced levels of glutamate, upregulation of inflammatory signals) (Krathwohl & Kaiser, 2004; Okamoto et al., 2007; Buch et al., 2007; Peng et al., 2008; Mishra, Taneja, Malik, Khalique, & Seth, 2010; Hahn et al., 2010; Lee et al., 2011; Peng et al., 2011; Hahn et al., 2012). During development, both neurons and macroglia derive from NPCs in the subventricular zone (SVZ) lining the central canal of the developing CNS. While most neurons in both rodents and humans are formed prior to birth, production of astroglia and oligodendroglia continues postnatally (Skoff, 1990; Skoff & Knapp, 1991; Lee, Mayer-Proschel, & Rao, 2000; Chan, Lorke, Tiu, & Yew, 2002; Geha et al., 2010). In humans, for example, oligodendrocyte formation and myelination continue well into the late teenage years, to accommodate CNS growth and maturation. While NPCs are obviously critical for CNS development, they are also present and functional in the adult CNS, although their characteristics, localization, and cell-specific markers are somewhat different from NPCs in the developing brain. In adults, *neuro*genesis is normally quite limited, occurring only in specific regions. In humans and other primates, these regions include the subgranular zone of the hippocampal dentate gyrus (DG) and the SVZ of the lateral ventricles (aka, ependymal/subependymal zones) (Kaplan & Hinds, 1977; Doetsch, Garcia-Verdugo, & Alvarez-Buylla, 1997; Eriksson et al., 1998; Kornack & Rakic, 1999). In vertebrates, including rodents, who are heavily dependent upon olfactory cues, neurogenesis within the adult SVZ results in a pool of cells that continually enters the “rostral migratory stream”, a migratory route specialized for the delivery of newly formed neurons to the olfactory bulb (Doetsch et al., 1997). A structure analogous to the rostral migratory stream remains to be validated in adult humans, although the pathway exists during development (Pencea, Bingaman, Freedman, & Luskin, 2001; Bhardwaj et al., 2006; Sanai et al., 2011; Wang et al., 2011). Unlike neurons, glia are normally formed throughout the lifetime of an animal, and glial progenitors undergo a constant, slow turnover throughout the adult CNS parenchyma (MESSIER, LEBLOND, & Smart, 1958; Imamoto, Paterson, & LEBLOND, 1978; Sturrock, 1979; Kornack & Rakic, 1999; Kornack & Rakic, 2001). Whereas neonatal NPCs proliferate routinely and robustly, adult NPCs in the SVZ and DG are mostly quiescent. They display somewhat different cell markers, and often respond to milieu signals or interact with surrounding cells differently than NPCs in young tissues. In response to exercise, injury/perturbation, inflammation, or other stimuli, adult NPCs can become more active, generating a subset of highly proliferative progenitors that can form neurons and/or glia that integrate into surrounding tissue (Thored et al., 2006a; Kernie & Parent, 2010; Wang, Plane, Jiang, Zhou, & Deng, 2011). Whether the enhanced turnover of adult NPCs after injury involves “active” adult NPCs or transit amplifying cells that derive from “quiescent” NPCs, or both, it is a somewhat different process from formation of cell populations in development, with different effectors and results (Romanko et al., 2004; Rola et al., 2006; Burns, Murphy, Danzer, & Kuan, 2009). Deficits in NPC populations appear to

contribute to diseases like Parkinson's, Huntington's, and Alzheimer's diseases, which involve specific neuron types (Curtis et al., 2003; Curtis et al., 2007; Crews, Patrick, Adame, Rockenstein, & Masliah, 2011), and to more global injuries such as stroke/ischemia and epilepsy (Parent et al., 1997; Thored et al., 2006b; Curtis et al., 2007; Ohira et al., 2010). Increased NPC proliferation is often assumed to indicate beneficial plasticity. However, proliferation must renew NPCs while also producing new neurons or glia (asymmetric division), and cell production must be balanced to tissue requirements. In Huntington's disease, for example, there is a loss of striatal neurons even though proliferation and SVZ size are significantly increased (Curtis et al., 2007; Kazanis, 2009), because the ratio of $GFAP^+$ glia (type B cells) produced is too high (Curtis, Waldvogel, Synek, & Faull, 2005). Increased proliferation may also be offset by death or aberrant migration, as in some epilepsy models (Parent et al., 1997).

The effects of HIV and/or drugs of abuse on adult hippocampal neurogenesis have been recently reviewed (Eisch & Harburg, 2006; Venkatesan, Nath, Ming, & Song, 2007). Accordingly, the discussion here will include other brain regions and gliogenesis. It will also include developmental studies, because of relevance to HIV acquired in the perinatal and adolescent periods. Since NPCs are uniquely positioned as the forerunners of CNS neurons and macroglia, the potential effects of NPC infection or dysregulation by HIV are extensive. For example, the evidence that $nestin^+$ or $Sox\text{-}2^+$ human NPCs can be infected by HIV (Lawrence et al., 2004; Schwartz & Major, 2006; Rothenaigner et al., 2007; Hahn et al., 2012) under conditions or in numbers that are disease-relevant remains controversial. In numerous experimental paradigms, HIV or HIV proteins have been shown to alter the proliferative and survival characteristics of NPCs. These include rodent (Khurdayan et al., 2004; Buch et al., 2007; Hahn et al., 2012) and human NPCs (Krathwohl & Kaiser, 2004; Mishra et al., 2010; Hahn et al., 2012) exposed in culture or *ex vivo* settings, NPCs within the brains of gp120 and Tat transgenic rodent HIV models (Okamoto et al., 2007; Lee et al., 2011; Hahn et al., 2012; Avraham et al., 2014), and in HIV postmortem brains (Krathwohl & Kaiser, 2004). In general, whether the models have examined NPCs from/in adult or developing systems, HIV or HIV proteins have been reported to depress NPC proliferation. This was also the case in human hippocampal slice cultures exposed to either X4 HIV coat proteins or to the CSF from HIV patients with dementia (Krathwohl & Kaiser, 2004). Alternatively, NPCs showed enhanced proliferation when exposed to medium from infected macrophages co-stimulated with LPS (Peng et al., 2008). Survival is variably reported as being unchanged by Tat, gp120, or HIV (Mishra et al., 2010; Lee et al., 2011; Hahn et al., 2012; Malik, Saha, & Seth, 2014) or reduced by Tat or gp120 (Buch et al., 2007; Avraham et al., 2014), feline immunodeficiency virus (van Marle, Antony, Silva, Sullivan, & Power, 2005), or by infection with a viral vector expressing HIV envelope (van Marle et al., 2005). The different outcomes likely reflect varied susceptibility among stages of differentiation (Levison, Rothstein, Brazel, Young, & Albrecht, 2000; Brazel, Nunez, Yang, & Levison, 2005). Changes in these parameters have the potential to alter the balance of mature cells that derive from the NPCs.

Exposure to HIV, HIV proteins, or milieu changes that occur in the HIV-infected brain might also redirect the lineage of undifferentiated cells. Normally, NPCs undergo a series of

self-renewing divisions prior to an asynchronous division that results in one daughter cell that is committed to a neuron or glial cell fate/lineage. HIV infection or viral protein exposure appears to skew NPC fate toward production of glia/astroglia at the expense of neurons and/or oligodendrocytes (Hahn et al., 2010; Peng et al., 2011; Hahn et al., 2012). Since viral production reportedly increases as infected NPCs differentiate into astroglia (Lawrence et al., 2004), cell lineage choices, i.e., the formation of astroglia at the expense of other NPC derivatives, may increase CNS consequences of NPC infection, including the potential for more latent virus in the CNS. This may be especially relevant in pediatric/adolescent patients given their larger and more mitotically active NPC population. Changes in the milieu can push more NPCs towards a particular lineage, for example, increasing glia or astroglia at the expense of neurons, which may explain the enhanced numbers of astroglia that we have seen in adult mice exposed to HIV-1 Tat for 3 months (Hahn et al., 2014). Increased astrogliogenesis also appears to be directly triggered by HIV-infected microglia both *in vitro* and in an infected SCID mouse model via a STAT3-dependent mechanism (Peng et al., 2011). While lineage redirection has not been directly demonstrated in the context of HIV, it has been well documented during development and in some diseases (Bithell, Finch, Hornby, & Williams, 2008; Sabo, Kilpatrick, & Cate, 2009; Lu et al., 2011; Ninkovic & Gotz, 2013).

HIV is a situation of reverberating inflammation. It is perhaps not surprising that HIV infection or viral protein exposure limits NPC proliferation, since brain inflammation is well known to impair neurogenesis (Monje, Toda, & Palmer, 2003; Ekdahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Moreno-Lopez et al., 2004; Whitney, Eidem, Peng, Huang, & Zheng, 2009; Lu et al., 2011). However, the relationship between inflammation and NPC function is nuanced. Endogenous ROS and nitric oxide may actually be necessary for NPC proliferation (Yoneyama, Kawada, Gotoh, Shiba, & Ogita, 2010), and the inflammatory milieu can inhibit, stimulate, and also influence the general direction of cell lineage (neuronal vs. glial), depending on the characteristics of the inflammation and the phenotype of the microglia involved in the inflammatory response (Butovsky et al., 2006).

### 5.1. Opiate and Opiate-HIV Interactions on Progenitors and Cell Populations

Morphine, which is a legal but regulated analgesic, is also an active metabolite of heroin (diacetylmorphine) and is used in many studies as a surrogate for heroin exposure/abuse. NPCs (nestin$^+$, Sox2$^+$; also GFAP$^+$ in adult) and their early derivatives (e.g. DCX$^+$/b-III tubulin$^+$ neurons; CD44$^+$/vimentin$^+$ young astrocytes; Nkx2.2$^+$/A2B5$^+$/O$_4^+$/Olig1$^+$/Olig2$^+$ young oligodendrocytes) express MOR, DOR, and KOR (Buch et al., 2007; Tripathi, Khurshid, Kumar, & Iyengar, 2008; Hahn et al., 2010). Furthermore, diverse agonists and antagonists for MOR, KOR, and DOR (e.g., heroin, morphine, β-endorphin, naltrindole, [D-Ala$^2$, D-Leu$^5$]-enkephalin (DADLE), β-funaltrexamine (β-FNA), naltrexone) (Eisch, Barrot, Schad, Self, & Nestler, 2000; Holmes & Galea, 2002; Persson et al., 2003; Mandyam, Norris, & Eisch, 2004; Koehl et al., 2008; Tsai, Lee, Hayashi, Freed, & Su, 2010) affect their proliferation and other behaviors. To date, most opiate studies have focused on adult hippocampal neurogenesis, and a number have included physical exercise as a parameter, which promotes neurogenesis partly via β-endorphin effects (Persson, Thorlin, Bull, & Eriksson, 2003). Interestingly, the reduced NPCs and neurogenesis seen in transgenic HIV-1

gp120 mice are normalized by exercise, although the role of endogenous opiates in this effect was not assessed (Lee et al., 2013). When exercise is removed from consideration, morphine reduces adult neurogenesis (Eisch et al., 2000; Mandyam et al., 2004; Kolodziej, Stumm, Becker, & Hollt, 2008; Arguello et al., 2008), even after controlling for glucocorticoid levels (Eisch et al., 2000), and MOR-null mice show a transiently enhanced post-injury neurogenesis in hippocampus (Kolodziej et al., 2008). Important new evidence shows that opiates used in addiction therapy, such as buprenorphine, may also reduce NPC formation in either the perinatal (Wu et al., 2014) or adult (Pettit, Desroches, & Bennett, 2012) CNS, disturbing the normal balance of glial populations through actions at MOR and/or the nociceptin/orphanin FQ receptors (Eschenroeder, Vestal-Laborde, Sanchez, Robinson, & Sato-Bigbee, 2012).

NPC proliferation is reduced by exposure to either HIV/HIV proteins or opiates independently, suggesting the potential for interactive, co-morbid effects of combined HIV and opiate exposure. Morphine interactively increases CNS inflammation in most HIV models (Perez-Casanova, Husain, Noel, Jr., Rivera-Amill, & Kumar, 2008; Bruce-Keller et al., 2008; El-Hage et al., 2008; Turchan-Cholewo et al., 2009; Bokhari et al., 2011; Dever et al., 2014), so it might be expected to exacerbate the effects of HIV on NPCs through generalized inflammation. However, as NPCs and their progeny express opiate receptors, there may be interactive effects that are independent of inflammation. Several studies have now shown that morphine exacerbates acute effects of HIV and Tat *in vitro* and in the developing brain. Our *in vitro* work has shown that combined exposure to morphine and Tat, or morphine and HIV, further depressed proliferation of murine and human NPCs and decreased NPC pools (Hahn et al., 2012). Morphine exposure in perinatal HIV-1 Tat-transgenic mice had a remarkably similar effect in vivo (Hahn et al., 2012). In human NPCs, this effect was shown to reflect a delay at the G1 phase of the cell cycle involving increased extracellular-signal regulated kinase-1/2 (ERK1/2) activation and concomitant increases in p21 and p53 (Malik et al., 2014). The ramifications of reduced numbers of NPCs, or an increased astroglial population at the expense of neurons and/or oligodendroglia, are likely to significantly impact cognitive and motor function. It remains unclear whether the chronic exposure to opiates that occurs in patients or drug abusers, either during development (neonates, adolescents) or in adult brains, can permanently alter CNS cell populations. The very critical question of whether the nature of opiate exposure might yield fundamentally different outcomes has also not been addressed. For example, do opiates administered for pain yield a different outcome than opiates that have been self-administered (resulting in dependence and addiction)? Studies that compare outcomes of contemporaneous exposure to opiates and HIV/HIV proteins versus the more “real life” situation where drug exposure occurs prior to HIV infection are also lacking.

### 5.2. Psychostimulant-HIV Interactions on Progenitors and Cell Populations

Among the psychostimulants both cocaine and amphetamine/methamphetamine exposure can influence NPC behaviors. Similar to opiates, in most studies cocaine exposure appears to inhibit the proliferation of human (Hu et al., 2006) and rodent (Lee et al., 2008) NPCs *in vitro* as well as in various perinatal and adult rodent models in vivo (Dominguez-Escriba et al., 2006; Lee et al., 2008; Garcia-Fuster, Perez, Clinton, Watson, & Akil, 2010; Yao, Duan,

Yang, & Buch, 2012). A number of mechanisms for these effects have been put forward, including down-regulation of cyclin A related to ER stress induced by cocaine metabolites (Lee et al., 2008), and changes in cytoskeletal-associated genes (Lee et al., 2009). In one study, exposure to cocaine during critical prenatal periods reduced normal numbers and disturbed radial migration of GABAergic and glutamatergic neurons in the neocortex of developing rats (Lee, Chen, Worden, & Freed, 2011), presumably in part through effects on NPCs. In the dentate gyrus of adult rats, both 8 d and 24 d exposure to cocaine decreased NPC proliferation, but did not affect survival or newly generated cells or their morphology, dendritic arborization, or localization in the areas examined (Dominguez-Escriba et al., 2006). These disparate findings are no doubt partly due to the inherently different properties of NPCs in developing and adult systems. Cocaine also reduced the motility of human NPCs *in vitro* through inhibition of CXCL12-to-CXCR4 signaling (Hu et al., 2006). Reduced motility is associated with downregulation of a transcription factor (SOX2) that supports progenitor phenotype, and the early differentiation of young neurons. Prenatal cocaine exposure also appears to have lasting, sex-specific effects on resident NPCs in adult brains (Patel, Booze, & Mactutus, 2012). In a genetic study with relevance to addicted individuals, cocaine had quite different effects on NPCs in two lines of rats bred to express different propensities for cocaine “abuse”. NPC proliferation was suppressed by chronic cocaine exposure in rats with low responses to novelty, but in rats with high novelty responses (enhanced sensitization/psychomotor response to cocaine) NPC proliferation was normal, as was the ratio of neurons-to-glia generated, although there was less survival of newly formed neurons (Garcia-Fuster et al., 2010).

The preponderance of studies show that methamphetamine or amphetamine exposure also reduces NPC proliferation and formation of new glia and/or neurons, although a few disparate outcomes may provide insight into important variables. The proliferation of both adult hippocampal and striatal progenitor cells *in vivo* is frequently assessed by 5-bromo-2′-deoxyuridine (BrdU) incorporation (a thymidine analogue incorporated during DNA synthesis) or Ki67 antigenicity (a nuclear protein associated with cell division) (Scholzen & Gerdes, 2000) in species including rats, mice, and gerbils (Teuchert-Noodt, Dawirs, & Hildebrandt, 2000; Mao & Wang, 2001; Mandyam, Wee, Eisch, Richardson, & Koob, 2007; Yuan, Quiocho, Kim, Wee, & Mandyam, 2011). Similar effects are seen *in vitro*, where survival is also variably reduced (Tian, Murrin, & Zheng, 2009; Venkatesan et al., 2011; Bento, Baptista, Malva, Silva, & Agasse, 2011). These effects have been correlated to enhanced nitration and modification of function of key metabolic proteins (Venkatesan et al., 2011). One report suggests that a single dose of methamphetamine at 14 d of age can result in reduced NPC proliferation in the hippocampus of adults (Hildebrandt, Teuchert-Noodt, & Dawirs, 1999). Another set of studies suggests that exposure to a neurotoxic dose of methamphetamine may temporarily increase activity of quiescent NPCs in the adult striatum, by effects mediated through dopamine D2 (but not D1) and neurokinin 1 receptors (Tulloch, Ghazaryan, Mexhitaj, Ordonez, & Angulo, 2011). These cells, most of which have glial phenotypes, contribute to an increase in the size of the striatum, but the increased glial population is not maintained in the absence of methamphetamine (Tulloch et al., 2011; Tulloch et al., 2014). The importance of the timing of drug exposure is highlighted in a study comparing self-administration in intermittent versus daily exposure (Mandyam et al.,

2008). Increased NPC proliferation was reported with intermittent exposure to methamphetamine, while daily exposure had the opposite effect. Interestingly, intermittent exposure also resulted in formation of more immature neurons, although there was no net neuron gain due to offsetting effects on later stages of differentiation. Daily exposure decreased all aspects of cytogenesis. Other extended access self-administration models also showed reduced NPC proliferation and decreased neuron and/or glial formation (Mandyam et al., 2007; Yuan et al., 2011).

There has been very little exploration of psychostimulant-HIV interactions on NPCs. In both a rat hippocampal NPC cell line, and in transgenic mice, HIV-1 Tat and cocaine reduced NPC proliferation without affecting NPC survival. These individual effects and a modest tendency towards interaction were reversed by platelet-derived growth factor-BB (PDGF-BB) through a mechanism involving both the transient receptor potential cation channel-C1 (TRPC1), and ERK/CREB and mammalian target of rapamycin (mTOR) activation (Yao et al., 2012).

## 6. CONCLUSIONS

Although considerable progress has been made during the last decade toward identifying molecular and cellular sites of HIV and drug abuse convergence in the CNS, and several new therapeutic strategies have emerged that may prove beneficial, much work remains to be done. The high degree of variability in the response among individuals to HIV alone reveals a highly complex chemistry between host and viral genetics, a complexity that is undoubtedly more convoluted by drug abuse-neuroAIDS comorbidity. Moreover, many of the events underlying drug-abuse-HIV neuropathological interactions occur only within specific cell types and/or at specific times during ontogeny, which adds greatly to the intricacy of the problem. A full appreciation of the mechanisms underlying drug abuse and neuroAIDS interactions will likely require an understanding of the interrelationship of gene networks, rather than individual genes.

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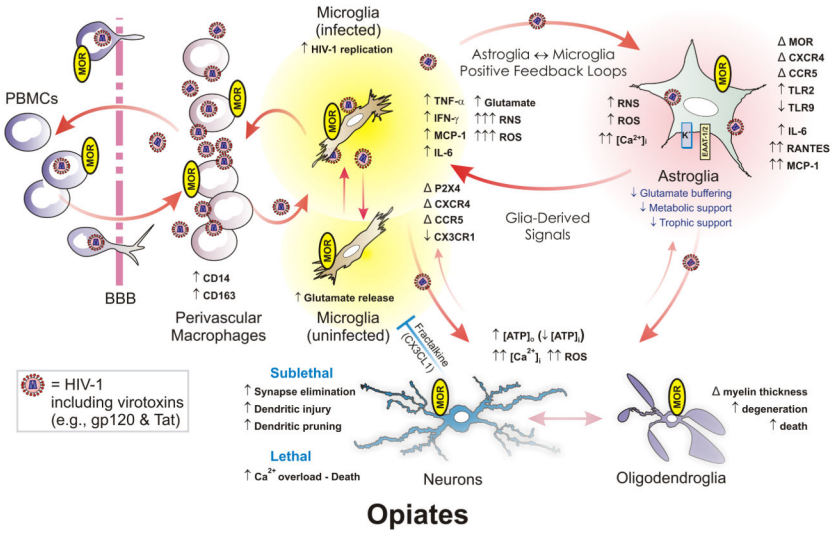


**Figure 1.**

Opiate drugs exacerbate HIV-1 neuropathogenesis through direct actions on glia—especially microglia and astroglia. Microglia are likely infected through interactions with infiltrating, perivascular macrophages, and propagate the bulk of HIV infection in the CNS. HIV-1 also infects astroglia, but to a far lesser extent, and perhaps without production of new virus., Infection results in the production of reactive oxygen and nitrogen species (ROS and RNS, respectively), pro-inflammatory cytokines, and the release of HIV-1 proteins such as gp120 and Tat. All of these promote inflammation and cytotoxicity in bystander neurons and glia. Opiate abuse alone can cause premature Alzheimer-like changes (Anthony et al., 2010) and morphine by itself can enhance neurotoxicity in vitro (Zou et al., 2011); however, opiates appear to potentiate many of the pathophysiological effects of HIV in the central nervous system of infected individuals. Multiple neuronal and glial types express μ-opioid receptors (MOR). Many of the neurodegenerative effects of opioid-HIV interactions are the result of direct actions on microglia and astroglia, which then lead to a positive feedback cycle of inflammatory/cytotoxic signaling between HIV-1-infected microglia and astroglia. Abbreviations: α-chemokine “C-X-C” receptor 4 (CXCR4); altered or changed (Δ); β-chemokine “C-C” receptor 5 (CCR5); blood-brain barrier (BBB); decreased (↓); fractalkine (CX3CL1); fractalkine receptor (CX3CR1); increased (↑); interferon-γ (IFN-γ); interleukin-6 (IL-6); intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$); intracellular sodium concentration ($[Na^{+}]_i$); monocyte chemoattractant protein-1 (MCP-1 [or CCL2]); peripheral blood mononuclear cells (PBMCs); regulated upon activation, normal T-cell expressed, and secreted (RANTES [or CCL5]); Toll-like receptor (TLR). Fractalkine released by neurons (and astroglia) can be neuroprotective by limiting the neurotoxic actions of microglia (blue “⊤”); red arrows suggest pro-inflammatory/cytotoxic interactions. Modified and reprinted from reference (Hauser et al., 2012) an “open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.5/), which permits unrestrictive use, distribution, and reproduction in any medium, provided the original work is properly cited.”

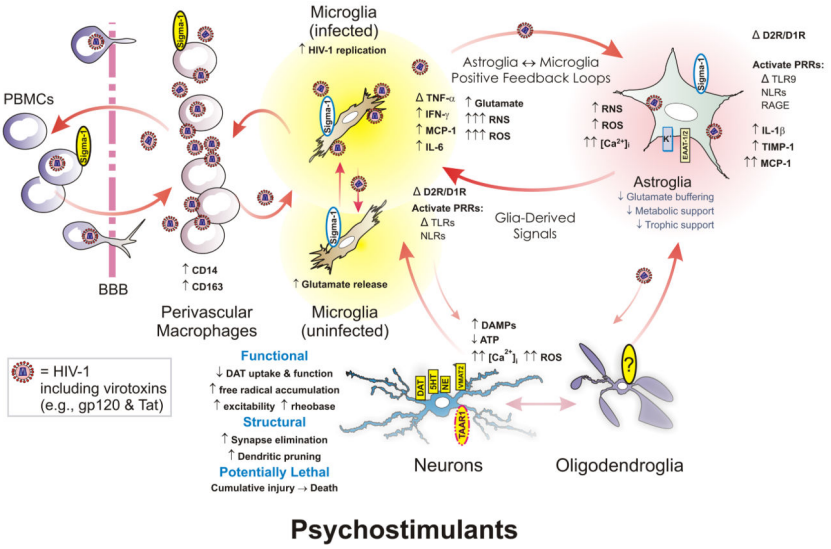


**Figure 2.**

Psychostimulants can increase synaptic damage through direct actions on neurons and glia, including both microglia and astroglia. Psychostimulants block dopamine, serotonin (5HT), and norepinephrine (NE) transport resulting in excessive accumulations of these neurotransmitters in the synaptic cleft. Dopaminergic neurons are particularly vulnerable to methamphetamine, which disrupts dopamine transporter (DAT) and vesicular monoamine transporter 1 (VMAT2) function and can damage presynaptic terminals of neurons. Synaptic injury is accompanied by the production of reactive oxygen (ROS) and nitrogen (RNS) species, and the production of damage-associated molecular patterns (DAMPs) that trigger activation of pattern recognition receptors (PRRs), including Toll-like receptor 9 (TLR9), nucleotide-binding oligomerization domain-like receptors (NLRs) and other PRRs (e.g., receptor for advanced glycation endproducts or RAGE) expressed by microglia and astroglia. Importantly, psychostimulants (especially methamphetamine) appears to activate neurons directly through the disruption of monoaminergic transporters and VMAT2 mentioned above and through the activation of trace amine-associated receptor 1 (TAAR1). Psychostimulants also disrupt glial function directly by increasing intracellular ROS and likely $Ca^{2+}$ concentrations ($[Ca^{2+}]_i$), NF-κB transcriptional activity, and by activating sigma-1-receptors (sigma-1; red, dashed-line outline), especially in the case of cocaine, and enzyme systems driving oxidative and nitrosative stress especially in microglia (and other cell types). Increases in NF-κB transcriptional activity result in increased microglial, and to a lesser extent astroglial, production of tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin-1β (IL-1β), and various other cytokines, as well as tissue inhibitor of metalloproteinase-1 (TIMP-1). Psychostimulants also obstruct the buffering of extracellular glutamate by inhibiting excitatory amino acid transporters-1/2 (EAAT1/2) and the conversion of glutamate to glutamine by inhibiting glutamine synthetase, as well as by limiting glucose metabolism in astrocytes. Collectively, neuronal injury and intensified glial activation promotes positive microglial-astroglial, and neuronal-glial feedback that cause spiraling increases in neuroinflammation and neuronal injury. If unrestrained, the cumulative insults result in lasting neurodegenerative changes. Modified and reprinted from reference (Beardsley & Hauser, 2014). Reprinted from Advances in Pharmacology, Vol. 69,

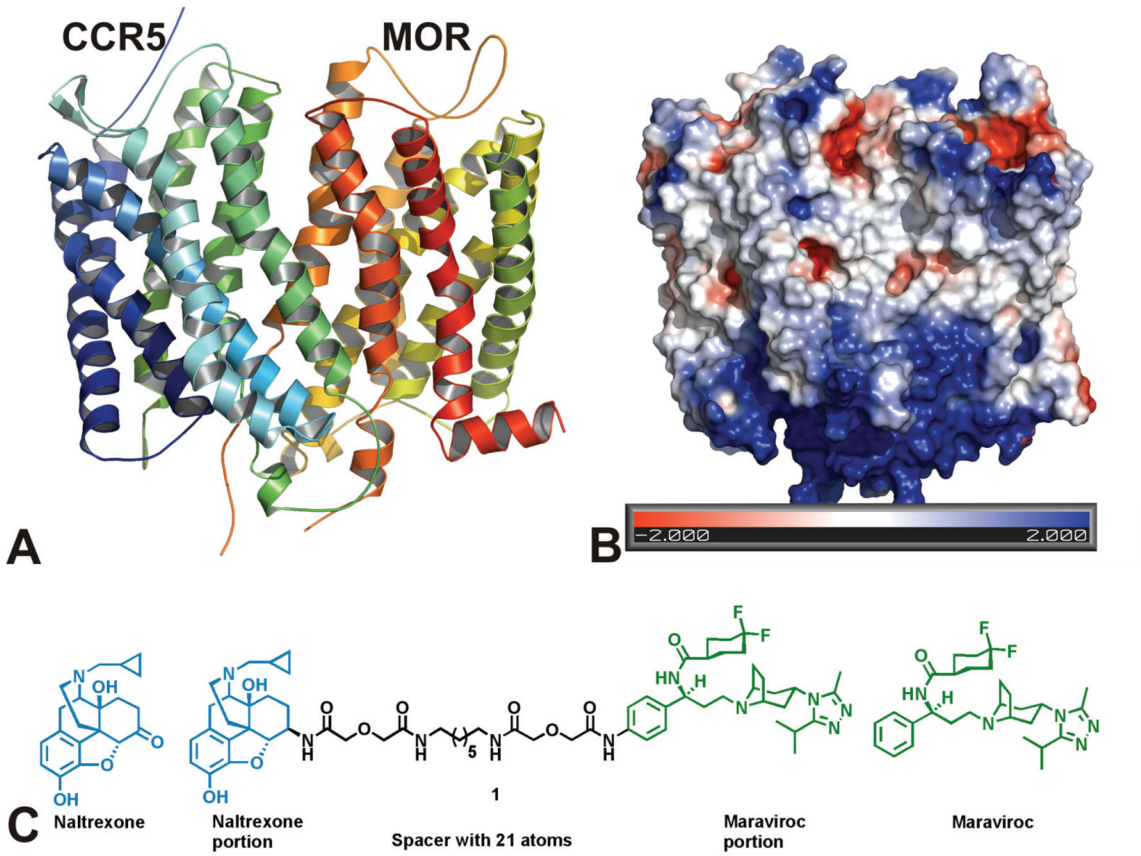


**Figure 3.**

Computer-generated model of a MOR-CCR5 dimer **(A)**. The helical portions colored in blue and green represent CCR5, while the red and yellow helices represent MOR **(A)**. Each ribbon was given an arbitrary color in order to distinguish individual helices from one another **(A)**. Representation of the Poisson–Boltzmann electrostatic potentials at the surface of the heterodimer using the APBS plugin by PYMOL (El-Hage et al., 2013) **(B)**. Acidic residues are shown in red (−2 kBT/e); basic residues are shown in blue (+2 kBT/e); white represents uncharged residues **(B)**. The model predicts that a majority of the interactions between the two receptors are hydrophobic **(B)**. Chemical structure of a bivalent ligand that binds both MOR and CCR5 receptors concurrently **(C)** (for complete description see, El-Hage et al., 2013). Reprinted with permission from Lippincott Williams and Wilkins/ Wolters Kluwer Health: AIDS (El-Hage et al.), copyright 2013.

**Table 1**

Examples of gene variants contributing to substance abuse that also correlate with the severity of HIV disease progression

| Neurochemical System | Gene | Variant (polymorphism/isoform | Outcome(s) measured | Finding/Interpretation | Selected Reference(s) |
|---|---|---|---|---|---|
| Dopamine | *Drd1* | *rs265975* | Drug dependence | Altered opiate/cocaine dependence | (Jacobs et al., 2013) |
| | *Drd2* | *multiple* | Drug dependence | Altered opiate/cocaine dependence | (Jacobs et al., 2013) |
| | *Drd3* | *rs6280TC* | Cognition | Increased cognitive impairment | (Gupta et al., 2011) |
| | *Drd4* | | Impulsivity | Altered inhibitory control | (Congdon, Lesch, & Canli, 2008) |
| | *SLC6A3(DAT1)* | | | Altered inhibitory control | (Congdon et al., 2008) |
| | *SLC6A3(DAT1)* | *3′UTR 40 bp* | HAND | No relationship to cognitive impairment | (Levine et al., 2012) |
| | *MAO1* | | | | |
| | *MAO2* | | | | |
| | *COMT* | *rs4680 (val158met)* | HIV serostatus | Significant correlation | (Sundermann et al., 2013) |
| | *COMT* | *rs4680 (val158met)* | HAND | No relationship to cognitive impairment | (Levine et al., 2012) |
| dopaminergic trophic factor | *BDNF* | *rs6265 (val66met)* | HAND | No relationship to cognitive impairment | (Levine et al., 2012) |
| Opioid | *OPRM1* | | HIV progression response to cART | Specific polymorphisms associated with HIV progression and response to treatment | (Proudnikov et al., 2012) |
| | *OPRM1* | *MOR-1K*<br>*MOR-1* | HAND and HIVE | ↑MOR-1K with HAND & HIVE; MOR-1 unaltered | (Dever et al., 2014) |
| | *OPRM1* | *MOR-1* | Susceptibility to drug [opiate?] overdose | | (Manini et al., 2013) |
| | *OPRM1* | *A C17T* | Drug use | | (Crystal et al., 2012) |
| | *OPRM1* | *MOR-1* | Drug use | MOR-1 isoform unaltered | (Crystal et al., 2012) |
| | *OPRK1* | | HIV risk | Specific polymorphisms associated with HIV progression & response to treatment | (Proudnikov et al., 2013) |
| | *OPKR1* | *KOR-1* | | ↑*OPRK1* in anterior cingulate; homeostatic attempt to decrease inflammation in exchange for motor impairment | (Yuferov, Butelman, Ho, Morgello, & Kreek, 2014) |
| | *PDYN* | | | ↓*PDYN* in anterior cingulate; homeostatic attempt to decrease inflammation in exchange for motor impairment | (Yuferov et al., 2014) |