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Molecular Targets of Opiate Drug Abuse in NeuroAIDS

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Abstract

Opiate drug abuse, through selective actions at μ opioid receptors (MOR), exacerbates the pathogenesis of human immunodeficiency virus-1 (HIV-1) in the CNS by disrupting glial homeostasis, increasing inflammation, and decreasing the threshold for pro-apoptotic events in neurons. Neurons are affected directly and indirectly by opiate-HIV interactions. Although most opiate drugs have some affinity for κ (KOR) and/or δ (DOR) opioid receptors, their neurotoxic effects are largely mediated through MOR. Besides direct actions on the neurons themselves, opiates directly affect MOR-expressing astrocytes and microglia. Because of their broad-reaching actions in glia, opiate abuse causes widespread metabolic derangement, inflammation, and the disruption of neuron-glial relationships, which likely contribute to neuronal dysfunction, death, and HIV encephalitis. In addition to direct actions on neural cells, opioids modulate inflammation and disrupt normal intercellular interactions among immunocytes (macrophages and lymphocytes), which on balance further promote neuronal dysfunction and death. The neural pathways involved in opiate enhancement of HIV-induced inflammation and cell death, appear to involve MOR activation with downstream effects through PI3-kinase/Akt and/or MAPK signaling, which suggests possible targets for therapeutic intervention in neuroAIDS.

Keywords

AIDS; chemokines; μ-opioid receptors; neurons; astroglia; microglia; neuroimmunology; CNS inflammation

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INTRODUCTION

Drug Abuse and HIV/AIDS as Interlinked Epidemics

Injection drug users are at higher risk for contracting HIV infection and for developing neurological and systemic complications. Injection drug use is a major risk factor and is the fastest growing means for spread of HIV infection in the United States (Beyrer et al., 2000; De Castro and Sabate, 2003; Francis, 2003; Vaswani and Desai, 2004). Patients who engage in high-risk sexual behavior frequently abuse drugs (Heckman et al., 1999; Miller, 2003). In addition to the drug abusing population, patients with HIV infection who develop persistent headaches or intractable pain syndromes associated with peripheral neuropathies require long-term use of opiate drugs for treatment. This group is therefore also at risk for any deleterious effects of HIV-opiate interactions (Mirsattari et al., 1999). Although methamphetamine, cocaine, and opiates (heroin, oxycodone) are detrimental in neuroAIDS, recent findings indicate that the opioid system intrinsically regulates the host CNS response to HIV. Moreover, current understanding regarding methamphetamine and cocaine in HIV progression have been recently reviewed elsewhere (Goodkin et al., 1998; Pellegrino and Bayer, 1998; Tyor and Middaugh, 1999; Nath et al., 2000; Nath et al., 2002). Recreational drug use appears to limit the immune system's ability to fight HIV (Nair et al., 2004). Unique aspects of opiate drug abuse-HIV interactions are emphasized in this review and key considerations for understanding the interactive effects are listed below:

- HIV/AIDS is a global pandemic with severe human and economic consequences.
- Drug abuse and HIV are interlinked epidemics—In the United States, AIDS is now largely spread through injection drug use or through the exchange of sex for drugs.
- Opiate drugs exacerbate the pathogenesis and neurological complications of HIV through direct actions in the CNS.
- Opioid-HIV interactions in the CNS are complex, and mediated through direct actions in neurons, astroglia, and microglia. Although occasionally reported to be beneficial, the net consequences of opioid actions in the CNS are deleterious.
- Opiate drugs act by disrupting the endogenous opioid system. Understanding how the opioid system modulates neuropathogenesis will be fundamental toward understanding neuroAIDS, and will provide insight regarding the potential role of endogenous opioids in neuroAIDS.

Opiate drug use and AIDS

Globally, 34–46 million people are currently infected with HIV (UNAIDS, 2003) and injection drug use is a major factor in the spread of the disease. HIV-1 infected opiate injection drug abusers undergo an accelerated rate of progression to AIDS and HIV dementia (Nath et al., 1999a). Not only does injection drug use increase the probability of contracting HIV (Nath et al., 1999a), but perhaps more importantly, opiate drugs intrinsically alter the pathogenesis of HIV. As noted, in addition to the drug abusing population, patients with HIV infection who develop persistent headaches or intractable pain syndromes can require long-term use of opiate drugs for treatment, thereby placing this group also at risk for any deleterious effects of HIV-opiate interactions (Mirsattari et al.,

1999). In addition to experimental findings, epidemiological studies are also beginning to establish links between opiate drug use and AIDS progression (Sheng et al., 1997; Donahoe and Vlahov, 1998), although the extent to which opiates per se contribute to AIDS progression has been controversial (Everall, 2004; Donahoe, 2004; Ansari, 2004). This may be in part due to the fact that the mechanisms underlying opiate-HIV interactions are incompletely understood (Everall, 2004; Donahoe, 2004). In studies of infected humans, drug histories are frequently not reliable, and patients have not been routinely screened for drug use or systematically screened for neurologic complications (Avison et al., 2003). Varying results are obtained depending on the parameter measured, the cell type affected, and timing of the insult. Since the consequences of drug interactions in peripheral organs may differ from those in the brain (Donahoe, 2004; Ansari, 2004), findings from periphery may not be readily extrapolated to the CNS (Nath et al., 2002). In fact, the CNS appears to be preferentially vulnerable to opiate drug-HIV interactions (Nath et al., 2002; Donahoe, 2004). Recent findings indicate that chronic opiate abuse increases viral load in the serum and CSF of non-human primates (Kumar et al., 2004) and causes significantly worse CD4 cell recovery in clinical studies (Dronda et al., 2004), suggesting the progression of the disease is markedly affected by opiates. Opiates also appear to increase perivascular B-lymphocytes in presymptomatic, HIV-positive individuals who preferentially abuse opiates (Anthony et al., 2004). Lastly, opiate drug use may promote the spread and pathogenesis of other diseases that hasten HIV infection. For example, morphine increases hepatitis C virus (HCV) replication and attenuates the antiviral effects of IFN-γ in Huh.8 and FCA-1 cells (Li et al., 2003). These effects are mediated through activation of NFκB and antagonized by both naltrexone and β-FNA suggesting they are mediated through opioid receptors and μ opioid receptors (MOR) in particular (Li et al., 2003). Although HCV has been detected in monocytic cells in the CNS and in cerebrospinal fluid of infected individuals, the consequences of HCV on CNS function are not fully understood (Morsica et al., 1997; Radkowski et al., 2002). Interestingly, individuals co-infected with HCV were more likely to have abused opiates or stimulants and tended to have more neurocognitive defects than individuals infected with HIV alone (Ryan et al., 2004).

Opiates and immune modulation

In this review, the plant alkaloids derived from the opium poppy will be referred to as opiates (e.g., opium, heroin, morphine) and the broader class of related endogenous peptides and receptors as opioids. Morphine is the major metabolite of heroin in the CNS and preferentially activates MOR (Sawynok, 1986). Opiates intrinsically modify immune function and have been proposed as potential cofactors in the pathogenesis of AIDS (Donahoe and Vlahov, 1998). This is based in part on the ability of opiates to modulate HIV propagation in immune cells (Carr et al., 1996; Nyland et al., 1998; Sharp et al., 1998a; Wetzel et al., 2000; McCarthy et al., 2001) and is upheld by recent evidence that opioids and chemokine receptors undergo heterologous, bidirectional cross-desensitization (Rogers et al., 2000; Rogers and Peterson, 2003). Morphine or the endogenous peptide β-endorphin (Sundar et al., 1995), which preferentially activate MOR, potentiate the expression of HIV in acutely infected peripheral blood mononuclear cells (Peterson et al., 1990; Carr and Serou, 1995), and this may result from the enhanced production of TGF-β (Chao et al., 1992; Peterson et al., 1993a; Peterson et al., 1993b). The endogenous peptide

endomorphin-1, which activates MOR, increases HIV replication in isolated human brain cells (Peterson et al., 1999). Although most opiate drugs with abuse liability activate MOR preferentially, some can activate DOR and KOR opioid receptors especially at high concentrations. Alternatively, selective MOR activation can alter the expression of DOR and KOR, as well as endogenous opioid peptides that act through all three receptor types.

Besides actions at MOR, activation of DOR and KOR can also modify HIV progression. Many of the components of the endogenous opioid system (peptides and receptors) can modulate the host response to HIV-1 infection (Adler et al., 1993; Sheng et al., 1997; Peterson et al., 1998; Rogers and Peterson, 2003). MOR, DOR and KOR can have different effects. For example, subsets of leukocytes express MOR, DOR, and KOR, as well as endogenous opioid peptides such as enkephalins, and opioids can modulate neuroimmune function through complex (direct and indirect) actions that involve both peripheral and central neural and non-neural mechanisms (Mellon and Bayer, 1998; Chang et al., 1998; Sharp et al., 1998b; Ignatowski and Bidlack, 1999; Bidlack, 2000; McCarthy et al., 2001). Although the effects of opioids on immune function have been previously reviewed (Adler et al., 1993; Sharp et al., 1998a; Bidlack, 2000; Peterson et al., 2001), an emerging concept is that the opioid system can have complex (positive and negative) effects on HIV infection and/or replication in immunocytes. For example, MOR stimulation increases HIV expression in monocytic cells (Peterson et al., 1993a; Peterson et al., 1993b; Peterson et al., 1999), while kappa receptor activation can have an opposing inhibitory effect on HIV expression in monocytic and lymphocytic cells (Chao et al., 1996; Peterson et al., 2001; Chao et al., 2001; Gekker et al., 2004). MOR and KOR have been noted to mediate opposing actions in other systems (Bohn et al., 2000). Interestingly, MOR activation can increase the expression of cytokine receptors that serve as co-receptors for HIV in susceptible cells including CCR3, CCR5, and CXCR4, while KOR stimulation can increase CCR2, while decreasing CCR5, expression (review (Rogers and Peterson, 2003)). To add to this complexity, as noted earlier, there is evidence for bi-directional heterologous interactions between opioid and chemokine receptors (Rogers et al., 2000; Rogers and Peterson, 2003; Chen et al., 2004). There is also evidence that opiate withdrawal markedly destabilizes immune function. Following opiate withdrawal, immune homeostasis is disrupted as characterized by a reduced ability to mount an immune response (Rahim et al., 2003; Rahim et al., 2004).

CNS complications related to HIV

Although AIDS is clearly a disease that affects multiple systems and cell types, it was appreciated very early that the CNS was highly vulnerable to HIV. Neurological complications of HIV infection may range from peripheral neuropathies to CNS infections and tumors (Avison et al., 2003; Estanislao et al., 2003). Of these complications, dementia is the most debilitating and is in part characterized by sub-cortical dementia accompanied by motor symptomatology including paralysis and ataxia (Berger and Nath, 1997; Factor et al., 2003). AIDS dementia complex (Navia et al., 1986b), HIV-1 associated cognitive-motor complex (Janssen et al., 1989), or HIV-1 associated dementia (HAD) (synonymous terms) are neurological syndromes that typically occur in conjunction with advanced immune suppression. Neurons, in particular, were an inevitable target of the disease despite findings

that the neurons themselves are normally not infected. Pathological correlates include neuronal loss (Everall et al., 1993), myelin pallor, reactive astrogliosis, dendritic pathology, and especially an increased presence of microglia and multinucleated giant cells (Navia et al., 1986a; Glass et al., 1993; Bell, 1998). The combined pathological changes are referred to as HIV encephalitis (HIVE). Mononuclear phagocytes (macrophages and microglia) are key cellular intermediaries in the neuropathogenesis of HIV. Monocyte/macrophages in the periphery become infected and subsequently cross the blood brain barrier (Trojan horse hypothesis) preferentially invading the parenchyma at perivascular sites (Meltzer et al., 1990; Persidsky and Gendelman, 2003). Although some infection of astrocytes and endothelial cells are reported, HIV is concentrated and retained in brain microglia and infiltrating macrophages (Wiley and Achim, 1994), which constitute a major cellular reservoir of HIV-1 in the brain (Nath, 1999; Kaul et al., 2001; Garden, 2002; Persidsky and Gendelman, 2003; Rock et al., 2004). Macrophages/microglia are the major site of production of new virions and toxic viral proteins (e.g., gp120, Tat) and the source of many toxic cellular products. Toxins released by microglia include cytokines such as tumor necrosis factor alpha (TNF-α), interleukins, platelet activating factor, as well as arachidonic acid, L-cysteine, glutamate, quinolinic acid, and nitric oxide (Persidsky and Gendelman, 2003).

Immune modulators contribute significantly to the pathogenesis of HIV infection (Poli and Fauci, 1992). Monocytes/macrophages are major contributors of cytokines. Infected macrophages show increased expression of TNF-α, TNF-α receptors, interleukin-1 (IL-1), interferon-γ and nitric oxide synthase (Tyor et al., 1992; Wesselingh et al., 1993; Sippy et al., 1995). Opioids can also behave as cytokines (Peterson et al., 1998), or modulate the response of leukocytes to cytokines (Rogers and Peterson, 2003), thereby mediating the host response to infection by acting as the chemical signal between immune cells and/or cells that intercede during the host response to infection. The neurotoxic properties of gp120 and Tat are in part mediated by their ability to induce inflammation and perhaps directly via cytokine mimicry (Murphy, 2001). Hence, opioids may modulate the response to virotoxins (and perhaps vice versa) by interacting with particular cytokine/chemokine receptor signaling pathways. Interactions likely occur at multiple levels. For example, MOR have been reported to heterodimerize directly with CCR5 chemokine receptors (Suzuki et al., 2002), although the functional significance of these interactions is not fully understood (Miller and Falke, 2004; Milligan, 2004)

Opiate Drug Abuse and neuroAIDS

Neurocognitive and motor dysfunction frequently occurs with HIV infection, and several prominent pathological studies indicate that patients with HIV infection and a history of opiate drug abuse are more likely to develop HIVE (Davies et al., 1997; Bell et al., 1998; Nath et al., 2002). Both HIV and opiate drug abuse increase the proportion of macrophages/microglia in the CNS (Bell et al., 2002), which likely sets the stage for subsequent pathophysiological change. Despite this, however, opiate-HIV interactions are incompletely understood and the degree to which opiate abuse *per se* contributes to the progression of AIDS is controversial (Everall, 2004; Donahoe, 2004). Varying results are obtained depending on the parameter measured, the cell type affected, and timing of the insult. In

studies of infected humans, drug histories are frequently not reliable, and patients are not routinely screened for drug use. As noted earlier, the consequences of drug interactions may be particularly deleterious in CNS (Donahoe, 2004; Ansari, 2004).

Opioid-HIV interactions in the CNS are highly complex, and although sometimes beneficial, most consequences of opiate abuse are deleterious. Although opiate use increases the progression to HIVE, the specific mechanisms underlying the accelerated neuropathogenesis remain uncertain (Nath et al., 2002). Neurons (Gurwell et al., 2001), astrocytes (Khurdayan et al., 2004), and microglia (Tomassini et al., 2004) express opioid receptors and each cell type displays unique responses to opiates and HIV alone or in combination. Experimental findings are supported by clinical studies. The presence of giant cells and/or HIV p24 immunoreactivity in the CNS was found more frequently in preferential opiate drug users (56%) than in non-drug-abusing homosexual men (17%) with AIDS (Bell et al., 1998). The findings are from a well-characterized cohort that is unique in the extent to which they preferentially abuse opiates. HIV-1 infected individuals who inject opiate drugs have been reported to undergo an accelerated rate of progression to HIVE and/or HIV dementia (Bell et al., 1998; Nath et al., 1999a; Nath et al., 2002; Arango et al., 2004). Not only does injection drug use increase the probability of contracting HIV (Nath et al., 1999a), but perhaps more importantly, opiate drugs may intrinsically alter the pathogenesis of HIV through direct effects on neurons and glia (Gurwell et al., 2001; Khurdayan et al., 2004; El-Hage et al., 2005). Although considerable evidence indicates that opiate abuse increases the HIV progression in the CNS, the mechanism by which opiates exacerbate CNS pathology and neurological complications are not understood. Relatively straightforward questions, such as are opiates per se acting principally on compromised neurons or infected glia to accelerate HIVE, remain unclear (Nath et al., 2002). Thus, there are multiple, compelling reasons to investigate the interactions between opiate abuse and HIV infection that accelerate neuropathogenesis. Efforts are only beginning to be directed toward answering these extremely important questions in the CNS, and toward understanding the cellular mechanisms underlying neuropathogenesis due to HIV infection alone and when superimposed with opiate abuse. It is important to consider past findings when exploring opiate-HIV interactions in the CNS, which include:

- Opiate-HIV interactions in the CNS are complex, and although some isolated effects may be beneficial, the net consequence of opiate drug abuse is deleterious.
- Although multiple opioid receptor types are expressed, the MOR is the principal site of action for opiate drugs with abuse liability. Most evidence thus far indicates that the neurotoxic effects of morphine alone or in combination with HIV are mediated by MOR.
- Neurons, astrocytes, and microglia can express MOR and MOR activation affects each cell type differently. Opiates and HIV have unique effects in each neural cell type.
- The collective CNS response to opiate drug abuse and HIV differs from the response of individual cell types. Defining the intercellular (glia-glia, glia-neuron) interactions and their integration is key to understanding how opiate drugs exacerbate neuropathogenesis.

- Neuronal dysfunction and death is caused by the accumulated direct and indirect effects of opiates and HIV.

MOR activation and neuronal death—convergence with Tat/gp120 proapoptotic cascades?

Most opioids with abuse liability are ligands for MOR, and MOR activation can affect cell viability (Grode and Murray, 1973; Meriney et al., 1985; Meriney et al., 1991; Goswami et al., 1998). Interestingly, depending on the cell type and opioid dosage, opioids can have paradoxical—neuroprotective or neurodegenerative effects (Meriney et al., 1985; Meriney et al., 1991; Faden, 1996; Goswami et al., 1998). Morphine or Met-enkephalin can inhibit neuron death in the avian ciliary ganglion (Meriney et al., 1985; Meriney et al., 1991). In a cell line transfected with MOR, the MOR agonist DAMGO ([D-Ala^2,N-Me- Phe^4,Gly^5-ol]-enkephalin) activates Akt-induced neuroprotection (Polakiewicz et al., 1998). Alternatively, morphine can be toxic to Purkinje cells (Hauser et al., 1994) and neuronal cell lines (Hu et al., 2002). Also, fentanyl-related compounds, which are highly selective μ-agonists can be neurotoxic (Sinz et al., 2000; Kofke et al., 2002). In other studies, μ-opioids are not overtly toxic but enhance cell losses when apoptosis is induced by other factors (Dawson et al., 1997; Goswami et al., 1998). For example, the μ-agonist morphiceptin enhances staurosporine or wortmannin-induced apoptosis in chick embryonic cerebral cortex neurons (Goswami et al., 1998). Together, the above findings suggest that opioid effects on cell death are variable and cell type specific. Importantly, we have described a pattern of synergism between morphine and Tat in causing the death of striatal neurons. Although morphine by itself is not toxic to striatal neurons in culture, it significantly potentiates Tat toxicity in uninfected striatal neurons (Gurwell et al., 2001; Turchan et al., 2002). The observation that opioid exposure can exacerbate viral protein induced neurotoxicity has important implications for the neuropathology of AIDS dementia and gives impetus to the exploration of intracellular mechanisms of opioid-virotoxin induced neurotoxicity.

Opioids were first described as modulating cAMP, opening K^+ channels, and closing Ca^{2+} channels. Opioids are also known to have excitatory actions in many cell types (Crain and Shen, 1990; Wang and Gintzler, 1994; Huang, 1995; Hauser and Mangoura, 1998). More recently, opioids have been tethered to intracellular signaling pathways that have direct bearing on cell survival. MORs are typical G-protein coupled receptors. They can also activate mitogen-activated protein kinases (MAPK), and some other phosphotyrosines (Georgoussi et al., 1997; Mangoura, 1997; Wilson et al., 1997; Mullaney et al., 1997; Hauser and Mangoura, 1998) through either Gβγ subunits and/or SH-2 adapter proteins (Wilson et al., 1997; Mullaney et al., 1997; Belcheva et al., 1998; Ignatova et al., 1999; Belcheva et al., 2002; Belcheva et al., 2003). Acute activation of opiate receptors activates Gαi/o and Gβγ subunits of GTP-protein coupled receptors, which inhibit adenylyl cyclase and cyclic AMP production, and activate phosphatidylinositol 3-kinase (PI3-kinase or PI3K) and PLC, respectively (Ai et al., 1999; Persson et al., 2003a). PI3K and Akt, in particular, are involved with MOR mediated modulation of apoptosis (Goswami et al., 1998; Polakiewicz et al., 1998; Goswami et al., 2000; Kim et al., 2001; Iglesias et al., 2003). Interestingly, and of importance clinically, chronic exposure of neurons to morphine, lasting from hours to days, gradually leads to molecular and cellular adaptations of most pathways that differ greatly from the acute effects (Nestler, 2001; Tan et al., 2003). Chronic morphine

activates ERK, c-jun-N-terminal kinase (JNK), and p38 MAPK (p38-kinase) pathways, as well as causing super-activation of adenylyl cyclase (AC) (Ma et al., 2001). Increased AC activity is accompanied by increases in PKA and CREB in some neuronal types. Many of these same pathways in T-lymphocytes are also affected by morphine, but with somewhat different effects on cell viability compared to neurons (Singhal et al., 2001; Singhal et al., 2002; Suzuki et al., 2003; Wang et al., 2003a). And although studies in other cell types reveal important potential mechanisms of opioid action, there are aspects of opioid signaling and their functional consequences that are specific to neurons and cannot be generalized to other cell types (Hauser and Mangoura, 1998; Tan et al., 2003).

As noted, both Tat and gp120 have been shown to be directly neurotoxic. Although the literature on Tat signaling in neurons is not extensive, Tat exposure alone does appear to modulate a number of intracellular pathways that can affect cell survival. PC12 cells exposed to Tat alone display altered PI3-kinase signaling with downstream effects on Akt, cAMP and CREB (Milani et al., 1998; Zauli et al., 2001). Interestingly, the PI3-kinase effects for short term (< 24 h) and more chronic (> 24 h) exposure were different, with more chronic exposure driving cells increasingly towards apoptosis. GSK3β, a downstream target for PI3-kinase-Akt signaling, is also activated by Tat, leading to neurotoxic events in neurons (Maggirwar et al., 1999b; Tong et al., 2001). Tat is known to induce p53 expression in neurons (Silva et al., 2003), although this effect may depend on the specific Tat sequence (Ariumi et al., 2001). Crosstalk between PTEN (phosphatase and tensin homolog deleted on chromosome 10) and p53 may provide another signaling avenue for affecting cell survival (Stambolic et al., 2001; Freeman et al., 2003). Tat can also signal through MAPK and/or ERK1/2 events in neurons (Menegon et al., 1997; Peruzzi et al., 2002). Interestingly, gp120 can also interact in neurons with several of these signaling pathways and intermediaries including MAPK (Leoni et al., 1997), p42-ERK/JNK (Lannuzel et al., 1997), p53 (Yeung et al., 1998), and GSK3β (Everall et al., 2002). Tat and gp120 can also both modulate intracellular Ca^{2+} levels through effects on IP_3-dependent stores. Taken together, the findings cited above show that HIV viral toxins and opioids both stimulate a variety of overlapping pathways that can affect neuronal survival.

Potential targets of opiate-HIV interactions to improve survival

Previous work has shown that neurons which die in individuals with AIDS dementia or HIVE show activation of post-mitochondrial events typical of apoptosis including activation of the effector caspase-3 (Kruman et al., 1998; James et al., 1999; Garden et al., 2002). Our own work has shown that opioids synergize with HIV neurotoxins in activating caspase-3 and/or promoting neuronal losses (Gurwell et al., 2001; Singh et al., 2004). Similar events are activated in other conditions involving neurodegeneration suggesting that some of these findings are broadly applicable to other neurodegenerative disorders. Numerous in vitro models have shown that caspase-3 inhibitors can stop or delay neuronal death, but interrupting caspase-mediated pathways may only delay death instead of preventing it. Interrupting apoptosis in its final stages, i.e., at the stage of caspase-3 activation, may not permit neurons to retain functional capacity. Intervention at early step(s) preceding apoptosis may maximize the opportunity to retain neurons and their function. Since neuronal loss in HIV involves multiple toxic agents, and since opiate drug exposure is a co-morbid

factor, several apoptotic intermediates are likely involved. Targeting sites where multiple toxic signaling pathways converge would be advantageous.

One likely target for therapy is the serine/threonine kinase Akt, or protein kinase B (PKB). Akt1/PKBα is the predominant isoform in most mammalian tissues including CNS (Kandel and Hay, 1999). Akt activation is associated with numerous examples of receptor-mediated cell survival induced by growth factors and cytokines including PDGF, IGF-1, NGF, M-CSF and IL-3 among others (Franke et al., 1995; Yao and Cooper, 1995; Songyang et al., 1997; Dudek et al., 1997; Kelley et al., 1999; Vaillant et al., 1999). Akt is activated by PI 3-kinases, largely through the binding of the major PI 3-kinase lipid product PI(3,4,5)P_3 to the plekstrin homology (PH) domain of Akt. Binding of PIP_3, and to a lesser extent PI(3,4)P_2, to the PH domain of Akt causes its translocation to the plasma membrane where Akt is phosphorylated on thr308 and ser473 by 3-phosphoinositide-dependent kinase 1 (PDK1) (Datta et al., 1997; Kandel and Hay, 1999; Cross et al., 2000). Once activated, it promotes survival by phosphorylating substrates involved in apoptosis (Yao and Cooper, 1995; Datta et al., 1997; Dudek et al., 1997; Cardone et al., 1998; Cross et al., 2000) (see Fig. 1). pAkt phosphorylates and inactivates BAD and caspase-9, thus limiting activation of the effector caspase-3. pAkt also inactivates members of the FOXO family of proapoptotic transcription factors (FKHR-L1, AFX, FKHR) whose activity drives apoptosis through multiple mechanisms, including activation of FasL and Bim, and repression of Bcl-6 (Birkenkamp and Coffer, 2003). pAkt also activates IKK-α, the kinase that regulates IκB, leading to activation of transcription factor NFκB which generally inhibits apoptosis via transcriptional regulation of a number of survival factors. A more recently described target for Akt is glycogen synthase kinase 3β (GSK3β). Akt inactivates GSK3β by phosphorylation at ser9. GSK3β has recently been implicated in a number of neurodegenerative pathologies including Alzheimer's disease (Kaytor and Orr, 2002) and can promote neuronal apoptosis through interference with the activation of neuroprotective transcriptional factors such as nuclear factor of activated T cells (NFAT) and heat shock transcription factor-1 (HSF-1), and modulation of cellular levels and localization of tau, MAPs, and β-catenin. Interestingly, both Tat and gp120 appear able to activate GSK3β and inhibitors of GSK3β such as lithium and valproate are able to ameliorate virotoxin-induced neuronal death (Maggirwar et al., 1999a; Everall et al., 2002; Dou et al., 2003). There is also increasing evidence for crosstalk between signaling pathways typically activated by MOR and other G-protein coupled receptors (ras/MAPK) and the PI3K/Akt/GSK3ß pathway (Chu et al., 1996; Duckworth and Cantley, 1997; Lopez-Ilasaca et al., 1997; Polakiewicz et al., 1998; Scheid et al., 1999; Tan et al., 2003; Jones et al., 2003). Such interactions could mediate synergistic opiate-Tat-induced neurotoxicity.

Further proof that Akt regulates cell survival can be seen in the effects of the tumor suppressor gene PTEN. PTEN is a lipid phosphatase that antagonizes PI 3-kinase by promoting dephosphorylation of PI(3,4,5)P_3 to PI(4,5)P_2, thus downregulating levels of pAkt. PTEN(−/−) and (+/−) cells exhibit high basal pAkt activity and are resistant to apoptotic induction to the point where transgenic animals are highly susceptible to lymphoma (Stambolic et al., 1998; Suzuki et al., 1998; Sun et al., 1999). Akt is an attractive target for therapeutic manipulation since it is an intermediary in multiple apoptotic pathways and promotes survival by effects on cytochrome-c signaling (through BAD and caspase-9),

Fas ligand-death domain induction (through FKHRL1), NFκB transcription and GSK3β phosphorylation. Experimental strategies using wild-type or constitutively active forms of Akt or v-Akt have rescued neurons and other cell types after survival factor withdrawal (Kennedy et al., 1997; Philpott et al., 1997; Songyang et al., 1997; Dudek et al., 1997; Crowder and Freeman, 1998) or other apoptotic stimuli (Khwaja et al., 1997; Rohn et al., 1998; Goswami et al., 1999). Since Akt can act at a premitochondrial portion of the pathway, it may also limit the activation of caspase-independent apoptotic pathways involving components that are released from mitochondria, such as endonuclease-G. Excitotoxic increases in Ca^{2+} and calcineurin activation are directly opposed by Akt, which inactivates BAD. In theory, any treatment that increases Akt activity could interrupt calcineurin-mediated activation of BAD.

Opiate-HIV interactions in astroglia

Astroglia are a significant target for HIV and their function is markedly impacted by the disease (Brack-Werner, 1999; Nath, 1999; Nath et al., 1999b; Wang et al., 2004). Astroglia can express MOR, DOR, and/or KOR (Stiene-Martin and Hauser, 1990; Eriksson et al., 1990; Eriksson et al., 1991; Stiene-Martin and Hauser, 1991; Ruzicka et al., 1995; Gurwell et al., 1996; Hauser et al., 1996; Stiene-Martin et al., 1998; Thorlin et al., 1998; Stiene-Martin et al., 2001), and there are regional differences in opioid receptor expression among astrocytes in different brain regions (Hauser and Stiene-Martin, 1991; Eriksson et al., 1992; Ruzicka et al., 1994; Ruzicka et al., 1995; Gurwell et al., 1996; Stiene-Martin et al., 1998; Thorlin et al., 1999). Activation of MOR, KOR or DOR causes cellular hypertrophy (Stiene-Martin and Hauser, 1991; Gurwell et al., 1996; Hauser et al., 1996). The reactive cellular hypertrophy is mediated by increases in intracellular Ca^{2+} ($[Ca^{2+}]_i$) (Gurwell et al., 1996; Hauser et al., 1996), and is accompanied by increased GFAP immunoreactivity and may mimic reactive astrogliosis in vivo (Hauser et al., 1996; Hauser et al., 1998).

There are mixed reports regarding the extent to which astrocytosis occurs in the CNS of opiate abusers (Gosztonyi et al., 1993; Oehmichen et al., 1996; Buttner et al., 2000; Anderson et al., 2003). An assessment of astrocytosis in the frontal lobes found increases in glial fibrillary acidic protein (GFAP) immunoreactivity in of HIVE subjects, but not in drug abusers or pre-AIDS individuals (Anderson et al., 2003). This is perhaps not surprising since astroglia are highly plastic and their response to insults may be transient and reversible, and may differ among brain regions. Also, microglia increases, which occur with opiate abuse, are not apparent in the frontal lobes, but are seen in the thalamus and to a lesser extent in the hippocampus (see below) (Tomlinson et al., 1999; Arango et al., 2004). Especially, with respect to opioids, the response to morphine and the expression of MOR, DOR and KOR by astroglia differs among brain regions, is developmentally regulated, and cell cycle dependent (Hauser and Stiene-Martin, 1991; Eriksson et al., 1992; Ruzicka et al., 1995; Stiene-Martin et al., 1998; Thorlin et al., 1999). Therefore, the response of astrocytes to opiates and HIV is also likely to differ among brain regions, with age, and may change dramatically with disease progression.

Opiates and HIV-1 Tat synergistically disrupt astroglial function

Findings that both MOR activation (Hauser et al., 1996), and Tat (Haughey et al., 1999), synergistically increase Ca^{2+} release from IP_3-dependent intracellular stores, and that the interactions can be blocked by the PI3K inhibitor LY294002, suggest that interactions occur at the level of $[Ca^{2+}]_i$ in astroglia (El-Hage et al., 2005). Synergistic increases in $[Ca^{2+}]_i$ were markedly suppressed by inhibiting IP_3-dependent increases in $[Ca^{2+}]_i$ and by inhibiting Ca^{2+}–induced Ca^{2+} release (CICR) from internal stores (El-Hage et al., 2005). Last, the MOR antagonist, β-FNA, and the PI3K inhibitor, LY297856, also completely blocked synergistic increases in $[Ca^{2+}]_i$. PI3K can influence $[Ca^{2+}]_i$ by modulating PLCγ activity or by regulating Ca^{2+} influx (Barker et al., 1999). Synergistic increases in reactive oxygen species are also evident following combined opiate-HIV exposure (El-Hage and Sullivan, unpublished). Our findings suggest that PI3K is acting downstream of the MOR and mediating Tat and/or Tat-morphine induced increases in $[Ca^{2+}]_i$. Striatal neurons and astrocytes display similar patterns of $[Ca^{2+}]_i$ responsiveness to opiates and HIV Tat (Hauser, unpublished).

Astroglial release of cytokines

Astrocytes are strategically positioned to monitor physiological changes within the extracellular space (ECS) (e.g., transmitter levels, ion fluxes) and maintain steady state within that compartment (Vargova et al., 2001; Sykova, 2005). By disrupting normal astrocyte function, opiate drug abuse likely subverts the ability of astrocytes to maintain steady state levels of neurochemicals within the ECS. Moreover, morphine can modify cytokine production by astroglia (Mahajan et al., 2002). This is worsened by HIV infection in which the ECS is further compromised by viral (e.g., HIV virions, gp120, and Tat) and toxic 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 et al., 1999b; Kaul et al., 2001; Garden, 2002; Persidsky and Gendelman, 2003).

There is considerable evidence that Tat can modulate chemokine release by astrocytes (Conant et al., 1998; Nath et al., 1999b), and more recent evidence that opioids modulate the response of astroglia to a Tat insult (Sheng et al., 2003). Morphine exposure exacerbates Tat-induced chemokine (MCP-1, RANTES, MCP-5) and cytokine (IL-6 and perhaps IL-12) production by astrocytes (El-Hage et al., 2005). Interestingly, morphine does not appear to induce novel cytokines to be released; rather, morphine furthered an existing response of astrocytes to Tat (El-Hage et al., 2005). TNF-α reportedly has a priming effect on RANTES production, which in turn triggers MCP-1, RANTES and IL-6 production (Ng et al., 1994; Oh et al., 1999; Luo et al., 2003). Interestingly, morphine-induced increases in Tat-evoked MCP-1, RANTES, and IL-6 production are not preceded by synergistic increases in TNF-α, suggesting that morphine's effects are not mediated by increases in TNF-α levels beyond those seen with Tat alone. Thus, morphine-induced increases in MCP-1, RANTES, and IL-6 seemingly occur through actions that are downstream of TNF-α. Morphine's effects on chemokine production appear to be mediated through MOR since β-FNA, but not nor-BNI, significantly attenuated the effects of morphine plus Tat on levels of MCP-1 and RANTES transcripts at 4 h and 12 h (El-Hage et al., 2005). Interestingly, and commensurate with the

concept that MOR and KOR can sometimes have opposing effects, KOR activation inhibits Tat-induced MCP-1 expression in human astrocytes (Sheng et al., 2003). These studies revealed an important temporal requirement that KOR be activated for 6 h or 24 h before suppression of Tat-induced MCP-1 increases were noted. This suggests that KOR activation represses MCP-1 production through alterations in gene expression, which is not evident if Tat and KOR agonists are given concurrently (Sheng et al., 2003; El-Hage et al., 2005). Conversely, MOR activation increases Tat-induced MCP-1 mRNA levels and protein release within 4 h, suggesting new genes are likely to be not involved in the acute response (El-Hage et al., 2005).

Opiate HIV interactions in microglia

The role of the endogenous opioid system in pain and in mediating inflammatory events in immunocompetent cells especially in the peripheral nervous system is well established (see (Machelska and Stein, 2000; Walker, 2003) for review). Opioid receptors are widely expressed on immune cells and opiates can function similarly to cytokines, modulating immune activities (Donahoe and Falek, 1988; Rouveix, 1992; Sheng et al., 1997; Peterson et al., 1998). Indeed, immune function is markedly altered with chronic opioid abuse (Donahoe and Falek, 1988; Novick et al., 1991). More specifically, considerable evidence now suggests that opioids affect immune responses directly within the brain (Sheng et al., 1997; Nelson et al., 2000; Dimitrijevic et al., 2000). Treatment of microglia with specific opioid ligands has been shown to alter their phagocytic (Peterson et al., 1995), chemotactic (Chao et al., 1997), and free radical producing properties (Hu et al., 1998; Liu et al., 2002), as well as other functions (Eisenstein and Hilburger, 1998), including cytokine production (Wetzel et al., 2000; Peng et al., 2000). Opiates can also induce apoptosis in macrophages (Singhal et al., 1998; Singhal et al., 2002). Opioid-induced changes in the function of microglial cells may have critical implications for HIVD, in which microglial activation is thought to play a prominent role (Tyor et al., 1995; Glass et al., 1995; Gray et al., 2001). Morphine interacts with gp160 to modulate apoptosis in monocytes (Kapasi et al., 2004). Bell and coworkers find that the number of microglia tend to be increased in a cohort of HIVE-positive drug abusers who preferentially use opiates (Tomlinson et al., 1999; Arango et al., 2004). The number of microglia in HIV seropositive drug abusers compared to non-abusers tended to greater depending on the brain region studied. In particular, trends toward increased numbers of microglia in the gray matter of the thalamus and to a lesser extent temporal hippocampus were evident in drug abusers, while drug abuse did not appear to increase microglia in the frontal lobe (Arango et al., 2004). Despite wide-spread evidence for opiate-HIV interactions in macrophages/microglia, the exact intracellular mechanisms whereby opioids alter microglial activation are unclear. However, it is known that macrophage/microglia activation with HIV infection is accompanied by free radical production (including superoxide, hydrogen peroxide, hydroxyl radical, and peroxynitrite), as well as the release of other toxic substances, and may be a major factor in the neuropathology (Gendelman et al., 1997; Nath, 1999; Xiong et al., 2000; Kaul et al., 2001; Persidsky and Gendelman, 2003). Assuming opiates exacerbate these effects; this would be an important mechanism by which opiates hasten the pathogenesis of the disease. We propose that microglial free radical production, and opioid-induced increases in free radical production, are very important to immune signaling and the promulgation of brain inflammation though

redox-signaling in microglia. Interestingly, a role for free radicals in the signal transduction machinery responsible for microglial activation has recently been proposed, and the term “redoxsignaling” has been coined to describe intracellular signaling that is dependent on free radical production [for review see (Forman and Torres, 2001; Droge, 2002)].

Opiate HIV interactions in glial precursors

Neural progenitors express several key chemokine receptors (Tran and Miller, 2003; Tran et al., 2004), including CXCR4 and CCR5, that are cofactors involved in HIV infection (Lazarini et al., 2000; Peng et al., 2004; Kao and Price, 2004). Multipotential neural progenitors can become infected with HIV-1 and serve as a viral reservoir (Lawrence et al., 2004). Interestingly, viral production increases if the infected neural progenitors are allowed to differentiate toward an astroglial phenotype (Lawrence et al., 2004). HIV exposure inhibits the proliferation of neural progenitors and this reportedly occurs through CCR3 and CXCR4 chemokine receptors (Krathwohl and Kaiser, 2004). In addition, opioid receptors are widely expressed by neural progenitors within the ventricular zone (Reznikov et al., 1999), the subventricular zone (Reznikov et al., 1999; Stiene-Martin et al., 2001), the cerebellar external granular layer (Hauser et al., 2003), and the subgranular layer of the dentate gyrus (Persson et al., 2003a; Persson et al., 2003b).

We have found that exposure to morphine and Tat viral protein causes the preferential death of glial precursors (Khurdayan et al., 2004). The toxic effects of morphine and Tat on glial precursors are synergistic, mediated by MOR, and accompanied by the activation of caspase-3 and an inability to exclude ethidium monoazide (Khurdayan et al., 2004). Further characterization of the affected cells indicates that a majority were dual-fated oligodendroglia-type 2 astroglia (O2A) progenitors (Raff et al., 1983; Fulton et al., 1992). Because a vast majority of the O2A progenitors in our cultures would have developed into oligodendroglia with further maturation, we speculate that cells committed to an oligodendroglial fate may be preferentially vulnerable to combined opiate-HIV-1 toxicity (Khurdayan et al., 2004). Although this was not confirmed at the limited survival times studied, oligodendrocyte numbers tended to be reduced and this might become significant with greater durations of exposure or increased time. Macroglia may possess life spans lasting years, suggesting that deficits in gliogenesis would only become evident with protracted time. Assuming glial progenitors are similarly lost in the CNS, macroglial numbers may be impacted with sustained exposure to opiates in the HIV infected CNS. Whether chronic opiate abuse contributes to the pathogenesis of neuroAIDS by reducing macroglial turnover and CNS dysfunction is uncertain; but warrants further study.

Opiate-HIV-induced changes in glia likely contribute to neurotoxicity

As noted throughout, an evolving concept is that opiate drug abuse exacerbates HIV-induced neurotoxicity through indirect actions mediated by glia in addition to the direct effects on the neurons themselves. The role of microglia in the pathogenesis of HIVE and HIVD are well documented.

Microglia significantly modify the response of neighboring cells (neurons and glia) to HIV (Nottet et al., 1995; Tyor et al., 1995; Glass et al., 1995; Gray et al., 2001; Rogers and

Peterson, 2003), Opiate-induced exacerbation of the macrophage/microglial response to HIV is likely to further contribute to neuronal dysfunction and their eventual demise. In preliminary studies, we have found that intrastriatally-injected Tat (25 μg) combined with continuous systemic morphine exposure (time-release morphine implant; 25 mg released over 5 days; NIDA) interacted significantly to increase the number of reactive microglia and astroglia at 7 days post-exposure (El-Hage, Wu and Hauser, in preparation). Although frank neuronal losses are not seen at 7 days in these studies, there are significant increases in caspase-3 activation in striatal neurons suggesting that there is impending death. Collectively, these preliminary findings in vivo suggest that opiates exaggerate HIV protein-induced reactive glial changes, which precede and likely contribute to neuronal losses.

Although astroglia are normally neuroprotective, this appears to be short-circuited by opiate and HIV exposure. We propose that several critical mechanisms are involved in the altered relationship between astrocytes and neurons. First, astrocytes lose the ability to provide neurons with metabolic and trophic support. Second, astrocytes directly drive neuron toxicity through release of inflammatory signals (ROS and chemokines/cytokines). There is a rapid loss in intracellular metabolic and ion homoeostasis within astrocytes. Tat and morphine (the major product of heroin in the CNS) appear to interact and synergize, affecting critical astrocyte parameters and functions $[Ca^{2+}]_i$ and increased ROS production. Besides disrupting astroglial function intracellularly, ROS derived from astroglia can have toxic bystander effects on neighboring neurons. A likely consequence of loss of ion homeostasis is an increasing inability to buffer extracellular potassium and glutamate, both of which would lower the threshold for excitotoxicity in neurons. Other intracellular responses which may be part of an internal astroglial defense mechanism, but which also have the potential to disrupt neuronal function, include alterations in transcription and expression of key regulatory molecules. This may include changes in expression of the glutamate transporters GLAST (EAAT1) and GLT-1 (EAAT2), which are affected by morphine (Ozawa et al., 2001; Mao et al., 2002) or HIV (Wang et al., 2003b), respectively. In response to combined morphine and Tat, astrocytes also release proinflammatory cytokines and chemokines, many of which can be directly neurotoxic (e.g., TNF-α, IL-6), while others recruit monocytes/macrophages (e.g., MCP-1, MCP-5, and RANTES) and activate microglia, which in turn likely contribute to neurotoxicity. Thus, astroglia potentially mediate a substantial portion of the enhanced neuropathology seen in HIV infected heroin abusers through two different yet related mechanisms.

Opioid antagonists and agonists have been proposed as a treatment for HIV dementia

Based on its ability to inhibit HIV-1 expression in CD4+ lymphocytes, Peterson and coworkers have proposed that naltrexone be used as an adjunctive therapy to HAART in the treatment of HIV (Peterson et al., 2001). Our findings showing that MOR agonists increase the release of inflammatory cytokines by astroglia (El-Hage et al., 2005), while augmenting the toxicity of HIV proteins in neurons (Gurwell et al., 2001), glial precursors (Khurdayan et al., 2004), and to a lesser extent astrocytes (Khurdayan et al., 2004), support the notion that opioid antagonists would be neuroprotective in neuroAIDS. MOR antagonists in particular should be beneficial; since we find that opiate synergism with HIV toxicity is almost exclusively mediated through MOR. In addition, based on findings that KOR agonists can

suppress viral replication and MCP-1 release by astrocytes, KOR agonists have also been proposed as potentially beneficial for neuroAIDS (Sheng et al., 2003). Based on the above experimental findings, opiate drugs with mixed agonist and antagonist properties would be predicted to modify HIV neuropathogenesis through complex actions at multiple opioid receptor types. For example, treatment with buprenorphine, which is a partial MOR agonist and KOR antagonist, and is currently used to treat heroin addiction, might actually negatively impact disease progression. Alternatively, mixed KOR agonists and MOR agonists/antagonists have been proposed as beneficial in the treatment of addiction and pain (Bidlack et al., 2000; Neumeyer et al., 2001), and may also be beneficial in treating neuroAIDS. Lastly, although the precise role of endogenous MOR peptides in neuroAIDS is not been firmly established, the possible use of therapies involving opioid receptor antagonists to limit endogenous opioid peptide-opioid receptor interactions in non-opiate abusing patients with neuroAIDS might eventually need to be considered.

The therapeutic value of these novel strategies for treating neuroAIDS needs to be further explored. There seems to be little doubt that chronic opiate abuse significantly modulates the progression of neuroAIDS and it is likely that opiates worsen disease outcome and contribute to the development of HIV dementia. Work during the past few years has led to significant advances in our understanding of the cellular mechanisms that underlie this synergy between HIV/HIV viral proteins and opiates. Most importantly, we are now in a position to propose novel therapeutic strategies for treating neuroAIDS which are being explored in multiple experimental settings.

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ABBREVIATIONS

AC	adenylyl cyclase
CXCR	alpha chemokine receptor
Apaf-1	apoptosis protease activating factor-1
CCL	beta chemokine ligand
CCR	beta chemokine receptor
DOR	δ-opioid receptor
β-FNA	β-funaltrexamine
CAD	caspase activated DNAse
JNK	c-jun-N-terminal kinase
CREB	cAMP response element-binding protein
EAAT2	excitatory amino acid transporter-2
ERK	extracellular-regulated kinase

GPCR	G-protein coupled receptor
GSK3β	glycogen synthase kinase 3β
FKHRL or FOXO	forkhead transcription factor
HCV	hepatitis C virus
HAD	HIV associated dementia
HIV	human immunodeficiency virus
HIVE	human immunodeficiency virus encephalitis
IKK	IκB kinase
IP3	inositol trisphosphate
IFN	interferon
IL	interleukin
[Ca2+]i	intracellular Ca2+
KOR	κ-opioid receptor
LDLRP	low-density lipoprotein receptor-related protein
mannose receptor	mannose R
MAPs	microtubule associated proteins
MAPK	mitogen-activated protein kinase
MCP-1 or CCL2	monocyte chemoattractant protein-1
NFκB	nuclear factor-κB
MOR	μ-opioid receptor
NO	nitric oxide
nor-BNI	nor-binaltorphimine
NFκB	nuclear factor κB
O2A	oligodendroctye-type-2 astrocyte progenitor cell
PI3-kinase or PI3K	phosphatidylinositol 3-kinase
PDK1	phosphoinositide-dependent kinase 1
PLCγ	phospholipase C-γ
PTEN	phosphatase and tensin homolog deleted on chromosome 10
PH	pleckstrin homology
PKA	protein kinase A
PKB, also known as Akt	protein kinase B
PKC	protein kinase C

RANTES	regulated on activation, normal T cell expressed and secreted
ROS	reactive oxygen species
Tat	transactivator of transcription
TNF-α	tumor necrosis factor-α

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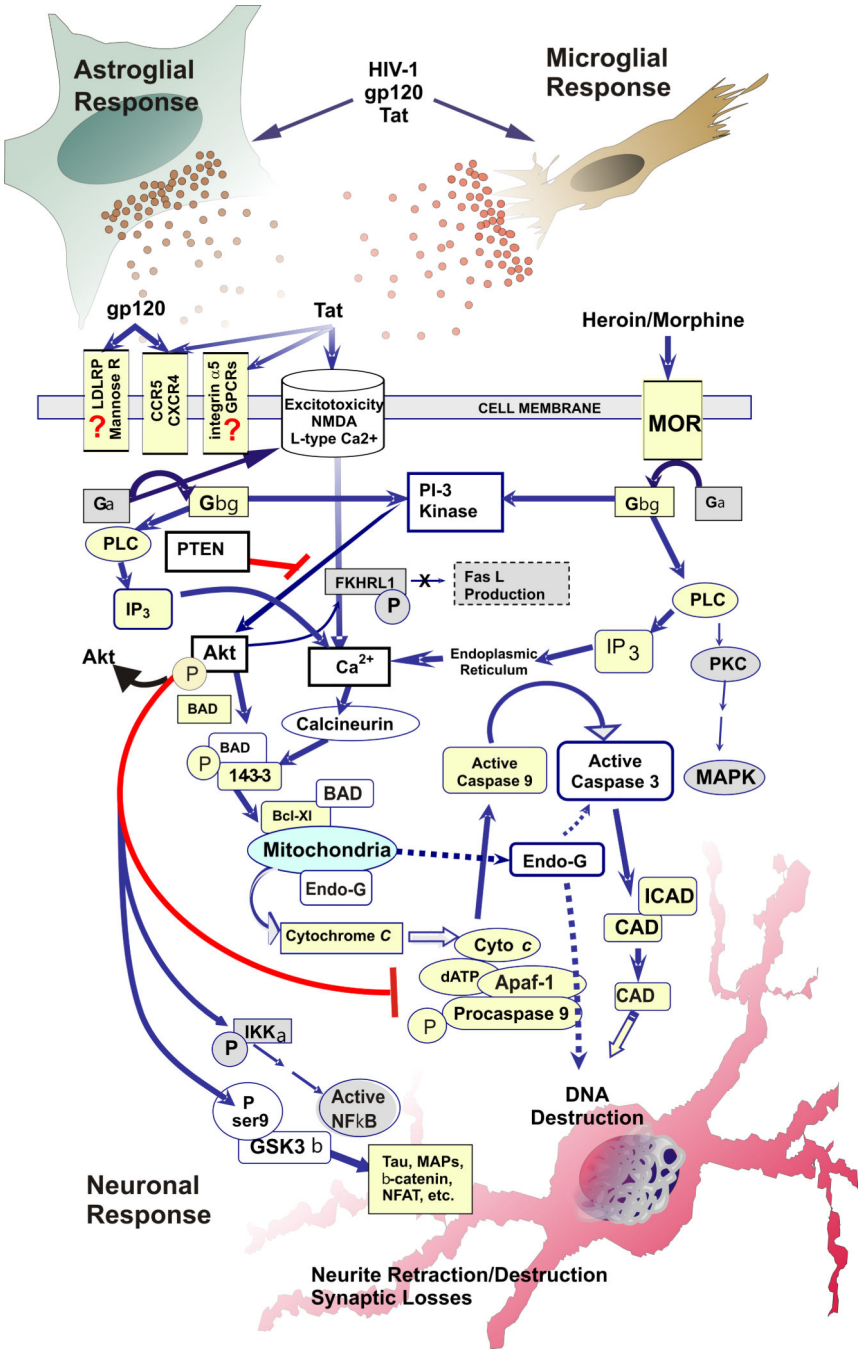

Fig. 1.

Pro-apoptotic signaling events that can be activated by opiate drugs and HIV, and potential sites of convergence underlying synergistic neurotoxicity. Potential sites where opioids impact Tat/gp120-mediated neurotoxicity include PI3-kinase, PTEN, Akt, Ca^{2+}, calcineurin, BAD, GSK3β, caspase-3 and endonuclease-G (endo-G) (arrows indicate activation; lines ending in "T" indicate inhibition; broken arrows indicate multi-step and/or incompletely understood pathways; pathways & abbreviations are noted in the text).

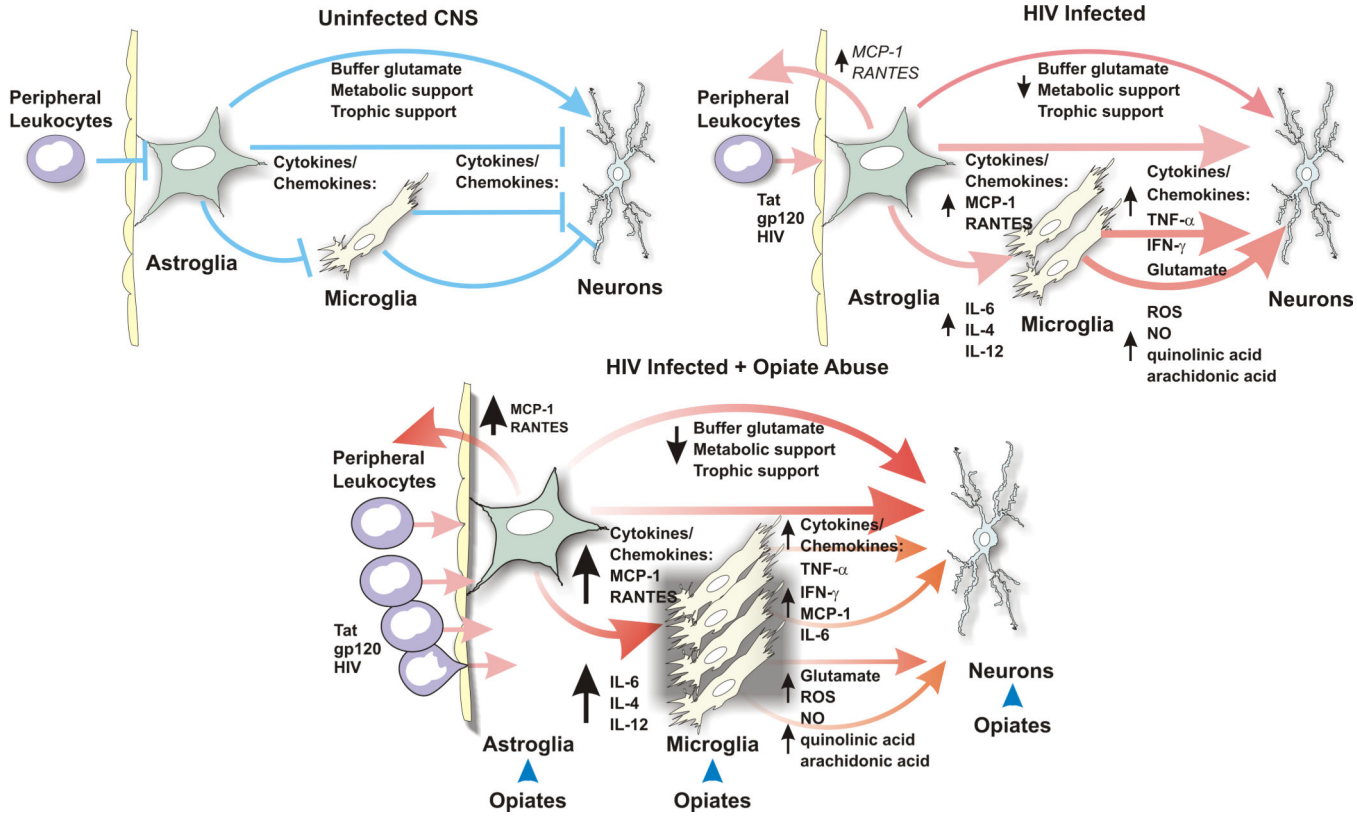

Fig. 2.

Summary of key intercellular events by which opiates may exacerbate the pathogenesis of HIV in the CNS. Opiates exaggerate the neuropathogenesis of HIV through direct actions on opioid receptor-expressing neurons, astrocytes, and microglia (blue arrowheads in “HIV-Infected + Opiate Abuse”). Note that opiates amplify the toxic actions of HIV, but do not result in additional insults. Opiates affect each cell type differently, which collectively results in disruptions in neuronal dysfunction and death. Leukocytes, within CNS blood vessels (Peripheral Leukocytes), including monocytes/macrophages and T-lymphocytes, can express opioid receptors and respond directly to opiates (arrows indicate intercellular signaling events; lines ending in a “T” indicate quiescent signaling; pathways & abbreviations are noted in the text).