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The role of Catecholamines in HIV Neuropathogenesis

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I. Introduction

Since the start of the pandemic in the early 1980's, HIV infection has been a major public health crisis across the world. Currently, around 37 million people are infected with HIV, with 1.8 million of them infected in 2016 alone. Although HIV-infection affects every region of the globe, the majority of infections are found in in sub-Saharan Africa and southeast Asia (UNAIDS 2017). Initially a terminal diagnosis, the advent of combinatorial antiretroviral therapy (cART or HAART) in 1996 dramatically improved the prognosis for HIV, enabling infection to be managed as a chronic condition rather than a terminal illness [1-3]. This therapeutic strategy treated patients with multiple (generally 3) antiretroviral drugs simultaneously, preventing escape mutations within the virus and thereby significantly improving the suppression of HIV replication. Successful cART has lengthened the lifespan and improved the quality of life for infected individuals. However, effects of cART have also created new health issues, as chronic infection and long-term exposure to antiretrovirals have created a suite of new metabolic, cardiovascular and neurologic disorders in infected individuals.

Even when HIV replication is fully suppressed with cART, around 50% of infected individuals still display a variety of neuropathological and neurocognitive sequelae known as NeuroHIV, or when referring specifically to the neurocognitive effects, as HIV-associated neurocognitive disorders (HAND) [1, 4]. While severe forms of neurocognitive impairment are rare in the cART era, the prevalence of HAND is increasing, and deficits in executive functioning, working memory, and psychomotor fluency are still frequently observed in HIV patients [2, 5, 6]. These can significantly impair therapeutic adherence [7] and accelerate the development of peripheral disease [8]. The development of these disorders is initiated by HIV infection of the central nervous system (CNS), which occurs in nearly all infected individuals shortly after initial infection [9, 10]. Within the CNS, the primary targets for HIV are myeloid lineage cells, such as microglia and perivascular macrophages. Infection of these cells is central to HIV neuropathogenesis, as infected myeloid cells generate new virions to further spread infection, and both infected and uninfected myeloid cells produce inflammatory mediators in response to infection [11-16]. The persistence of neurocognitive

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impairment in virally suppressed individuals suggests subclinical alterations in neurotransmission, neuronal and immune function may underlie the earliest manifestations of NeuroHIV in the cART era [17-23].

Dysregulation of catecholaminergic neurotransmission, particularly the dopaminergic system, has long been correlated with the development of neuroinflammation and HAND. Studies specifically examining role of catecholamines in HIV pathogenesis, particularly focused on NeuroHIV, are relatively few. However, over the course of the epidemic, researchers found that infected individuals show a number of catecholaminergic changes. These include increased damage in dopaminergic regions of the CNS, altered autonomic nerve activity, changes in catecholamine metabolism, stress induced changes in infection and response to cART, and altered viral replication and dysregulated immune responses resulting from changes to catecholaminergic tone [19, 24-48]. Further, data show that catecholamines, particularly dopamine and norepinephrine, are important mediators for neuroimmune crosstalk [47, 49-53]. As the dysregulated immune response is central to the etiology of NeuroHIV, these data suggest that disruptions in catecholaminergic tone in response to HIV infection, drug abuse, stress or specific therapeutic drugs, could exacerbate HIV neuropathogenesis. The dearth of studies in this area, particularly those dissecting the mechanisms by which catecholamines mediate their effects on NeuroHIV, has hindered our ability to understand and effectively treat these components of HIV neuropathogenesis. Therefore, this review will discuss what is known about the role of catecholamines in the development of NeuroHIV. We briefly discuss the state of CNS infection in the cART era, touching on the specific effects in dopaminergic and adrenergic systems, and then discuss catecholamine biology and what is known about the catecholaminergic systems in immune cells. We will then focus on catecholaminergic modulation of HIV infection and neuroinflammatory processes, and how these effects might enhance the development of NeuroHIV. The neurologic complications of HIV are a growing problem within the infected population, making the development of new neuroprotective strategies a pressing medical need. This review will contribute to a better understanding of the bidirectional interactions between catecholamines and HIV infection of the CNS, leading to novel therapeutic targets for the treatment of NeuroHIV.

II. HIV neuropathogenesis in the cART era

Prior to the widespread use of cART, HIV infection of the CNS commonly resulted in significant neuropathology including HIV encephalitis (HIVE), meningitis, microglial nodules, multinucleated giant cells, reactive gliosis, and neuronal injury and death [12, 34, 54, 55]. Severe neurocognitive impairment was also common, with HIV-associated dementia (HAD) found in 15-20% of infected individuals. Significant neuropathology was often coincident with neurocognitive impairment in many infected individuals, but the relationship between neurological damage and cognitive impairment is not entirely causal. Studies demonstrated that HIVE did not explain all HIV-associated dementia, and the best correlate for the development of HIV-associated neuropathology was myeloid cell activation in the CNS [16, 34, 56]. With cART, HIVE and HAD are almost nonexistent, and severe forms of neurocognitive impairment are rare, but the prevalence of mild and asymptomatic forms of neurocognitive impairment have increased, and HAND is still found in 40 – 70% of HIV

infected individuals [1, 4, 57-59]. Despite suppression of HIV replication below the limit of detection, fully suppressed individuals still show signs of NeuroHIV, and data show no correlation between neuropathology, neurocognitive impairment, and CNS viral load [23, 58-63]. This indicates that the development of HIV-associated neurological disease does not derive solely from damage associated with actively replicating virus [64-66].

NeuroHIV is initiated by HIV crossing the blood-brain barrier (BBB) to enter the CNS. This is thought to occur primarily via the transmigration of infected CD14+CD16+ monocytes [67], using the monocytes as “Trojan Horses” [68], although some studies suggest alternate routes of entry [69]. These mature CD14+CD16+ monocytes, are enriched in people with HIV and are more susceptible to HIV infection [67, 70]. The enrichment of this population is maintained in the presence of cART treatment [71], and is important to the development of HAND due to the disproportionate transmigration of CD14+CD16+ cells into the CNS [67, 72, 73]. Within the CNS, infected monocytes differentiate into perivascular macrophages and shed new virions, which infect additional macrophages and microglia. In addition to being the primary target for HIV infection in the brain [11-15], myeloid cells are the primary reservoir for HIV in this compartment [74, 75]. Astrocytes are infected at low levels [79, 80], and pericytes may also be infected [81], but the role of these cells in neuropathogenesis is unclear.

Although T-cells are the primary focus of HIV in the periphery, in the CNS the primary cells involved in neuropathogenesis are myeloid cells. This is because relatively few T-cells are present in the CNS, and these mostly surveil brain regions outside the parenchyma [76-78]. Increased T-cells, particularly CD8+ T-cells, are found in the brains of HIV-infected drug abusers and those with CNS-immune reconstitution inflammatory syndrome[47]. Polymorphonuclear neutrophils (PMNs) are the most abundant immune cells in the blood and can contribute to chronic immune activation during HIV infection [82]. However, PMNs do not seem to be infected by HIV [83] and their role in HIV-neuropathogenesis is not clear. Because the cells primarily targeted by HIV are T-cells and macrophages, these cells will be the focus of the remainder of this review.

In healthy individuals, CNS macrophages and microglia act as the primary immune response within the CNS, communicating with neurons by releasing a variety of cytokines and neurotrophic factors important to neuronal health and function [84-87]. Infection of these cells dysregulates production and release of inflammatory cytokines and neurotoxic viral proteins, activating neighboring uninfected cells and inducing further production of factors that perpetuate the neuroinflammatory environment. Infected or activated myeloid populations are thought to be primary drivers of neuroinflammation, and prior to cART, development of dementia correlated with myeloid cell activation [14, 15, 56]. Even with cART, immune activation is a critical component in the development of neurologic disease [88]. Infected brain tissue from cART-treated individuals shows upregulated CD68+ expression, as well as CD16 and CD163 positivity, indicative of significant macrophage and microglia accumulation and activation [66]. Soluble factors of monocyte activation, CD14 and CD163, are increased in the plasma and cerebrospinal fluid (CSF) of HIV+ individuals with neurocognitive impairment [89-92]. Activated monocytes and macrophages produce a number of inflammatory factors including cytokines (IL-6, IL-1β, TNF-α, interferons),

chemokines (CCL2, CXCL8, CXCL9, CXCL10), hydrolytic enzymes (matrix-metalloproteinases), and oxidative mediators (nitric oxide) [93, 94]. Production of these and other inflammatory and cytotoxic factors is thought to be central to the neuropathology of HIV infection in cART treated individuals [1, 14, 16, 34, 95].

Overall, while cART has significantly prolonged life and ameliorated HIV-associated disease, HIV infection of the CNS still induces a number of cognitive, behavioral and motor symptoms, along with substantial neuropathology. Data show that the inflammatory processes driving neurological disease persist in the individuals using fully suppressive cART [66, 88, 95-98], indicating that these processes are mediated by interactions distinct from viral replication. Over time, the damage from this chronic inflammation accumulates, interfering with neurotransmission and dysregulating neuroimmune communication. Many of these issues overlap with neurological issues associated with aging, and the synergy between these problems is growing [58] as the age of the HIV-infected population increases. Further, the ability to suppress but not eliminate HIV has resulted in an increased focus on the insults initiated by chronic infection and neuroinflammation, and the resultant changes in neurotransmission and CNS homeostasis.

IIa. The CNS viral reservoir

Reservoirs, are cell populations or anatomical sites that enable HIV to avoid the immune response, and are the primary impediment to eradication of HIV within an infected individual [99]. The importance of reservoirs is shown by the fact that HIV viremia recurs rapidly following interruption of suppressive cART [100, 101], and HAND occurs even in individuals on uninterrupted, suppressive cART therapy [2, 59, 61]. This suggests the CNS reservoir established prior to cART treatment may play an important role and is supported by studies identifying the lowest measured CD4 cell count, CD4 nadir, as one of the best predictors of neurocognitive impairment [102, 103]. As CD4 nadir generally corresponds to a period of unchecked viral replication, during which CNS invasion and establishment of the viral reservoir occur, the importance of CD4 nadir could indicate that some portion of CNS viral insults may be permanent. This is further supported by studies demonstrating lower CD4 nadir is associated with greater long-term decreases in subcortical gray matter and total white matter volume [104-107]. Although the most commonly studied reservoirs are long-lived CD4+ memory T-cells, many studies show that the CNS, which is an immune privileged site, is also often considered to be a reservoir [99, 108]. Post-mortem brain tissue from pre-symptomatic HIV-infected individuals showed HIV-1 gag DNA in parenchymal macrophages and microglia despite the absence of HIV p24 expression [109]. Another study found the amount of HIV DNA in peripheral blood mononuclear cells (PBMC) correlates with the severity of HAND [110], and the follow-up showed patients with HAND maintained high levels of HIV DNA in activated monocytes throughout a five-year course of cART [111]. While these and other studies do not clarify whether the CNS reservoir is latent or active [75], there is substantial evidence showing that the CNS reservoir exists in long term infected perivascular macrophages and microglia [99, 108, 112], which can support HIV-infection for long periods without cytotoxic effects [113-115].

IIb. Dopamine in HIV Neuropathogenesis

The involvement of the dopaminergic system in HIV neuropathogenesis has been hypothesized since very early in the epidemic. In the pre-cART era, elevated neuropathology was found in dopaminergic brain areas including the caudate and putamen, the substantia nigra and the prefrontal cortex (PFC) [12, 24-26, 30, 56, 58, 116-118]. In brain tissue from HIV-infected individuals, dopamine-rich brain regions such as the basal ganglia show the greatest degree of HIV-associated neuroinflammation [18, 95]. These regions also showed increased numbers of infected cells, and greater amounts of viral RNA [12, 28, 117, 118]. These effects were corroborated in simian immunodeficiency virus (SIV) infected macaques treated with L-DOPA and Selegiline to increase CNS dopamine levels. The increased dopamine in these animals significantly increased CNS viral load and exacerbated neuropathology [31, 32]. HIV infection and exposure to viral proteins also interferes with dopamine transporter expression and function [38, 119, 120], and dopaminergic neurons are particularly vulnerable to HIV-induced neurotoxicity [35, 121, 122]. Treatment with cART has shifted regional neuropathology, but patients still show substantial damage to dopamine-rich regions, including striatal dysfunction, increased inflammation, neuronal damage, and diminished resting state functional connectivity [123-128]. PET scans of cART treated HIV-patients with no history of illicit drug use found increased microglial activation in the basal ganglia [129]. High expression of HIV is still seen in these regions [28, 130], as is accumulation of HIV-infected microglia [131]. Additional studies which are discussed below also show specific effects of dopamine HIV infection and myeloid-mediated neuroinflammatory functions.

Polymorphisms in dopamine related genes, and changes in dopaminergic gene expression are also seen during HIV infection. Autopsy data from HIV+ patients have revealed correlations between dopaminergic gene expression and inflammation, suggesting that inflammatory mediators might be linked to dopamine signaling in HIV [19]. Several studies have connected genetic alterations in dopamine receptors (DRD) to neurocognitive impairment. Failure to downregulate the DRD2L gene is associated with unfavorable neuropsychologic and neuropathologic outcomes [19]. The rs6280TC single nucleotide polymorphism (SNP) in DRD3 is correlated with increased rates of cognitive impairment in HIV+ methamphetamine addicts [132], and several SNPs in DRD1 and DRD2 correlated with cognitive function in HIV+ drug abusers [133]. A strong correlation between a specific allele of the dopamine transporter (DAT), DAT 10/10, and HIV infection was found in German and African cohorts of HIV-positive and negative individuals. Individuals with the DAT10/10 allele, whether or not they were infected, showed higher baseline levels of CSF dopamine, suggesting that elevated dopamine is involved in HIV infection [134]. They also showed these changes in CSF dopamine and HIV infection were not correlated with genetic polymorphisms in catechol-O-methyltransferase (COMT, Val158Met), an enzyme involved in catecholamine metabolism, and dopamine receptors DRD2, DRD3, and DRD4 [135], although the specific DRD polymorphisms investigated were not the same as those mentioned above. Interestingly, the Val158Met polymorphism in COMT, while not associated with increased HIV infection, was found by separate groups to be associated with deficits in executive function and prefrontal activity in HIV infected individuals [136, 137].

Infection with HIV may also interfere with dopamine metabolism, thereby altering dopamine concentrations in the CNS. Infected individuals and SIV-infected macaques show decreases in CSF dopamine [27], increased DOPAC, and decreased homovanillic acid (HVA) in the CSF [43, 138]. Studies show decreased CSF dopamine levels and neuronal degeneration in dopaminergic brain regions of HIV patients [42, 139, 140]. This is supported by experiments in SIV-infected macaques showing decreased dopamine and tyrosine hydroxylase (TH)-positive neurons, as well as increased DOPAC in putamen [141]. However, more recent studies from this group found increased CSF dopamine in HIV patients during asymptomatic infection prior to cART initiation [142, 143]. In these studies, CSF dopamine was inversely correlated with CD4 cell counts, suggesting that elevated dopamine may be associated with disease progression [142, 143]. Using behavioral testing, these dopaminergic changes can be detected as dysfunction of frontostriatal circuits that reflect HIV-associated dopaminergic abnormalities [17, 126, 144]. Examination of brain tissue from HIV-infected individuals shows abnormal expression of dopaminergic synaptic proteins in striatum [33] and PFC [19], perhaps reflecting an adaptive shift in response to elevated dopaminergic tone. Together, these data suggest that HIV infection is still facilitated in a dopamine-rich environment. Further, the increase in infection damages dopamine neurons and neuronal structures, interfering with dopaminergic neurotransmission, even in individuals on effective cART. This interference could alter dopaminergic tone in different regions of the CNS, exacerbating the effects of dopamine on HIV infection in these regions and may play a significant role in the development of NeuroHIV.

IIc. Impact of Drug Induced Dopamine in HIV Neuropathogenesis

Unlike the interactions of catecholamines and HIV, the effects of drug-abuse on HIV neuropathogenesis are well studied [145-150], but it is important to mention them as almost all abused substances increase CNS dopamine [151-159]. Thus, the effects of dopamine on HIV infection are particularly important for HIV-infected drug abusers, who constitute 10 – 20% of the HIV-infected population worldwide [160-165]. While there is disagreement in the literature about the direction and specific impacts of drug abuse on HIV infection, it is generally agreed that drugs of abuse can synergistically disrupt dopaminergic transmission [24, 122], and can to alter the development of HAND [166-168]. This suggests HIV-infected drug abusers would be particularly susceptible to dopamine-mediated changes in neuropathogenesis, as the dopaminergic brain regions specifically affected by drugs of abuse, particularly the basal ganglia, are the regions in which exacerbated neuropathology has been found in the presence of dopamine. Indeed, HIV+ individuals with a history of illicit drug use show increased neuropathology and encephalitis at autopsy [170-174], and in the cART era, drug-abuse history remains one of the best predictors of neurocognitive decline [168, 173, 175-180]. Thus, use of illicit drugs, or of therapeutics that disrupt the dopaminergic system, could exacerbate the development of NeuroHIV in drug using HIV+ populations. A major caveat regarding many studies which clearly show an impact of drug abuse on distinct stages of HIV infection and HIV infected cells, is that these experiments are not necessarily examining the impact of dopamine on HIV infection. One issue with these types of studies is that many of them, in both animal models and humans, examine peripheral pathogenesis [181-184]. As addictive drugs exert the majority of their dopaminergic effects within the CNS and dopamine cannot cross the BBB, the mechanisms

involved are not likely mediated by elevated dopamine. Similarly, there are many studies which show potentiation of HIV infection by addictive drugs *in vitro*, in various immune cell types [185-189], particularly human macrophages [190-193]. These studies have provided a tremendous amount of useful information, but a significant caveat for this type of research is that it is generally performed in monoculture systems. It is not known whether treatment of macrophages or T-cells *in vitro* with drugs such as morphine or cocaine elicits a dopamine response, and it is not likely that the response would be the same as that generated by *in vivo* exposure of dopamine neurons within the central nervous system. Despite these caveats, the data still demonstrate that use of illicit drugs, or of dopaminergic therapeutics, could exacerbate the development of NeuroHIV by disrupting the dopaminergic neurotransmission in the CNS. Therefore, developing an improved understanding of the reciprocal interactions by which dopaminergic dysfunction and HIV-associated neuropathogenesis exacerbate each other will be critical to future therapeutics required in the developing HIV epidemic.

IId. Adrenergic Catecholamines in HIV Neuropathogenesis

The interaction of the adrenergic system with HIV neuropathogenesis has been studied far less than the interactions of dopamine and HIV. Studies show significant neuroinflammation and atrophy occurs in HIV-infected brain regions encompassing the CNS adrenergic system, such as the brainstem and pons [194-197], with elevated HIV RNA in the hippocampus proper [118]. However, HIV associated-neuropathology in specific adrenergic brain regions such as the locus coeruleus remains undetermined. Early in the epidemic, prior to cART, Glasgow and colleagues found significant adrenal pathology in HIV-infected individuals [198]. In the cART-era, the hippocampus remains significantly impacted, with increased myeloid cell activation [95, 199] and decreased hippocampal volumes [200], and no studies have specifically examined adrenergic brain regions in HIV-infected individuals on cART.

Most of the studies that have examined the adrenergic impact on HIV infection focus on the interactions with sympathetic nervous system (SNS) or the hypothalamus-pituitary-adrenal (HPA) axis. These studies show that the SNS and/or HPA axis are dysregulated in HIV-infected individuals, with decreases in norepinephrine during stress response [39], and hypo-reactivity of the autonomic system and HPA axis [41, 201]. There is a direct correlation between constitutive autonomic nervous system activity and HIV plasma viral load [45], and elevated stress levels, autonomic nervous system activity and norepinephrine are correlated with a poorer response to cART therapy [202, 203]. These studies suggest that the release of the adrenergic catecholamines, particularly norepinephrine, could enhance HIV infection, providing a pathway by which stress or other adrenergic stimulators might impact systemic HIV pathogenesis [40, 46, 204]. This is corroborated by a more recent study which also found that higher levels of peripheral norepinephrine correlate with accelerated disease progression, represented by increased plasma viral load and decreased CD4 counts, over a 4-year period [205]. These studies indicate that disruptions in adrenergic signaling may be important in the development of systemic infection, but that much more work needs to be done in this area.

Studies specifically examining norepinephrine in the context of NeuroHIV are rare, although Dever and colleagues recently found an increase in β-adrenergic receptor gene expression in

frontal lobe white matter and/or frontal cortex from HIV-positive individuals with combined neurocognitive impairment and HIV encephalitis [206]. In SIV-infected macaques, enhanced stress reduced survival [207, 208], and SIV replication was enhanced in close proximity to elevated catecholamine levels present in catecholaminergic varicosities [48]. In rodents, the HIV envelope protein gp120 interferes with the β-adrenergic receptor mediated function of microglia and astrocytes [209]. Thus, in the CNS, elevated norepinephrine could exacerbate HIV infection activation of myeloid β-adrenergic receptors, which are increased in the infected brain. As both norepinephrine and epinephrine are increased with stress, a common issue in HIV-infected individuals, these changes may exacerbate both peripheral and CNS infection in a significant proportion of the HIV-infected population. Unfortunately, the data on this subject are quite sparse, and the full effects of adrenergic catecholamines on both the HIV infection process and the associated inflammatory effects remain relatively undefined. To better treat both long term HIV infection and the chronic diseases associated with it, it is important to further define the role of adrenergic catecholamines in HIV infection.

III. Catecholamines

Catecholamines are monoamines, organic compounds containing a catechol ring (ortho-dihydroxybenzene) linked to an amino side-group. Dopamine, norepinephrine or noradrenaline, and epinephrine or adrenaline are catecholamine neurotransmitters derived from the amino acid tyrosine. Catecholamines are synthesized in their cognate neurons, both in cell bodies and in the nerve terminals. From there they are rapidly transported and stored in the endoplasmic reticulum or in vesicles along dendrites and at synaptic terminals [210, 211]. The release and reuptake of these molecules is highly-regulated through complex mechanisms, which act independently or in conjunction with other regulatory mechanisms. These molecules play vital roles in the modulation of behavior, metabolism, autonomic function, and immunity, acting in both the periphery and the CNS [212]. In the CNS, dopamine, norepinephrine, and to a much lesser extent epinephrine enable interneuronal communications that modulate neuronal activity and influence behavior. While the majority of studies on the actions of catecholamines have been performed in neurons, recent studies show that all catecholamines also have immunomodulatory actions. These occur in a number of different immune cell types, including T-cells, myeloid cells and neutrophils, and has been widely reviewed [47, 213-218]. Although these and many other studies clearly demonstrate an immunoregulatory effect of catecholamine interaction with immune cells, it is important to note that many of them used pharmacologic levels (10^{-6}M and higher) of catecholamines or catecholamine receptor agonists/antagonists. Therefore, it is not entirely clear how human immune cells in the CNS, where catecholaminergic concentrations remain unclear, respond to catecholaminergic stimulation *in vivo*. Further, during HIV infection, these effects may be changed by HIV-associated disruption in catecholaminergic tone.

IIIa. Catecholamine Signaling and Metabolism

Catecholamine metabolism is a critical step in the regulation of activity, as the amount of catecholamine to which a receptor is exposed is controlled by a) reuptake through DAT or the norepinephrine (NET) transporter, and b) synthesis and degradation of the catecholamine. All catecholamines are derived from tyrosine, and are synthesized through a

series of enzymatic reactions, beginning with the rate-limiting step, the conversion of tyrosine to L-DOPA by TH (Figure 1). Dopamine is then synthesized from L-DOPA by the action of DOPA decarboxylase, and then either released or hydroxylated by dopamine β-hydroxylase (DBH) to form norepinephrine. The final step in catecholamine biosynthesis is the conversion of norepinephrine to epinephrine by phenylethanolamine-N-methyltransferase (PNMT). There are also a number of pathways by which catecholamines can be catabolized, which are primarily mediated by COMT and monoamine oxidase (MAO), although additional enzymes are active in several stages of the catabolic cycle (Figure 1).

The actions of all catecholamines are mediated through their cognate receptors, dopamine or adrenergic receptors, which are members of the G-protein coupled receptor superfamily [219]. Dopamine receptors are divided into two groups, D1-like (D1 and D5), which couple to $G_{\alpha s/olf}$, and D2-like (D2, D3, D4) which are coupled to $G_{\alpha i/o}$ [219, 220]. Canonically, D1-like receptors activate adenylate cyclase, increasing intracellular cAMP, while D2-like receptors inhibit adenylate cyclase, blocking intracellular cAMP production [219-221]. These receptors can also signal through alternative pathways, the most prominent being mobilization of intracellular Ca^{2+} and activation of protein kinase C (PKC) through activation of phospholipase C (PLC). These pathways are thought to be mediated by either the Gq/11 protein coupling to D5 or D1:D2 heteromers, or by D2-like dopamine receptors signal through $G_{\beta\gamma}$, although the specific mechanisms remain controversial [222-224]. Another pathway exclusively activated by D2-like receptors acts through β-arrestin 2 to regulate the activity of Akt and glycogen synthase kinase 3-α/β (GSK3β) [219, 225]. Adrenergic receptors are also divided into two subgroups, α and β, and can be further subdivided into α_1, α_2, β_1, β_2, and β_3 receptors [226]. Each of the α receptors has distinct pharmacology, with the α_1-receptors coupled to $G_{\alpha q}$, and stimulating PLC, while α_2-receptors are coupled to $G_{\alpha i}$, inhibiting the production of cAMP [227]. All β-adrenergic receptors couple to $G_{\alpha s}$, meaning that activation stimulates the production of cAMP [228, 229]. Interestingly, data also show that in some circumstances, β_2-receptors may also couple to $G_{\alpha i}$, inhibiting cAMP production and potentially interfering with the effects of other β-adrenergic receptors [230].

IIIb. Catecholaminergic System in Immune Cells

Over the past two decades, the data has found that many types of immune cells, including both myeloid cells and T-lymphocytes, express all five dopamine receptors, as well as all the α and β adrenergic receptors. Human monocytes, monocyte-derived macrophages (MDMs) [52, 231, 232] and microglia express mRNA for all five dopamine-receptor subtypes, with the exception of D5 not being found in microglia [233]. We have shown D1, D2, D3 and D4 expression in the MDM plasma membrane, and other studies have also identified dopamine receptors on monocytes by flow cytometry [231, 232, 234-237]. Analysis of mRNA expression and surface proteins also confirm expression of all five dopamine-receptor subtypes in T-cells, although D1-like receptor expression is low and not consistent between studies [234, 238-241].

Expression of adrenergic-receptors on immune cells has been more widely studied than dopamine-receptors. Immunoblotting and pharmacologic assays show human monocytes and macrophages express functional $\alpha_{1,}$ $\beta_{1,}$ and β_2 receptors [242-249]. These cells respond functionally to stimulation by α_2 specific agonists [244, 250], however expression of α_2 receptors has not been established. The presence of functional adrenergic receptors in human microglia has not been confirmed, but mRNA and pharmacologic data indicate that $\alpha_{1,}$ $\alpha_{2,}$ $\beta_{1,}$ and β_2 receptors are present in rat microglia [251, 252]. T-lymphocytes also express mRNA and protein for $\beta_{1,}$ β_2 and β_3 receptors [241, 253]. Pharmacological studies and ligand-binding experiments also indicate that T-cells express α_2 receptors [254, 255], but expression of α_1 receptors has not been established.

In addition to expression of dopamine and adrenergic receptors, many immune cells express TH, DAT, and the vesicular monoamine transporter 2 (VMAT2) [236, 241, 256, 257]. Although expression of NET is undefined in human cells, NET and MAO-A expression was shown in rodents in a subset of macrophages called sympathetic neuron–associated macrophages (SAMs) [258]. Our data also show that MDM express both the genes (2A) and proteins (2B) for the majority of the enzymes involved in the metabolism of catecholamines, including MAO-A and B, COMT and very small amounts of DBH (Figure 2). Gene expression of PNMT was not found (data not shown). The purpose of immune catecholaminergic systems is not clear, but in T-cells, dopamine acts in an autocrine fashion to regulate both proliferation and TGF-β production [241, 259], and dopamine, but not norepinephrine or epinephrine, blocked a PKC-mediated induction of TH mRNA expression [257]. Elderly human microglia were found to be able to take up and release dopamine after K+ stimulation [233], and catecholamine uptake and release was shown in human PBMC [49, 241, 257, 259, 260]. These data indicate that immune cells can produce, release and metabolize of catecholamines, supporting the concept that these processes are immunoregulatory.

IIIc. Distribution of Catecholamines in the Central Nervous System

The catecholamines found in the central nervous system are primarily dopamine and norepinephrine, while the majority of epinephrine is found in the periphery. Epinephrine has been reported in a small number of brainstem neurons with projections to the thalamus and spinal cord, but very little is known about these neurons [261, 262]. Both dopamine and norepinephrine mediate their effects through volume transmission, acting on distinct brain regions to regulate a number of critical CNS functions. The pathways by which these catecholamines interact with different brain regions are described in Figure 3. As dopamine and norepinephrine are the predominant catecholamines present in the CNS, they are the primary catecholamines influencing the development of NeuroHIV and will be the focus for the remainder of this review.

In the CNS, dopamine is synthesized in dopaminergic neurons of the ventral tegmental area (VTA) (mesocortical and mesolimbic projections), substantia nigra (nigrostriatal projections), and arcuate nucleus of the hypothalamus (tuberoinfundibular pathway) [263]. Dopaminergic projections from the VTA ascend via the median forebrain bundle to innervate cortical and limbic regions. The mesocortical pathway projects to the prefrontal

and cingulate cortices and plays major role in cognition, motivation, and emotional response. The mesolimbic pathway projects to the nucleus acumbens, medial PFC, amygdala, and hippocampus to mediate reward-based habits, emotions, and cognition. Dysregulation of this pathway by dopaminergic stimuli plays a major role in the development of various addictions. The nigrostriatal pathway ascends from the midbrain substantia nigra pars compacta (SNpc) to striatal nuclei (caudate and putamen) in the forebrain to modulate production and coordination of movement. Dopaminergic neurons of the tuberoinfundibular pathway project from the arcuate nucleus to the median eminence and release dopamine into the hypophyseal portal system, regulating the release of prolactin from the anterior pituitary. Norepinephrine is predominantly synthesized in the locus coeruleus, as well as the lateral tegmental area of the brainstem. Neurons from the loci coerulei innervate a number of different CNS regions, releasing norepinephrine by volume transmission to modulate alertness and arousal. As mentioned, epinephrine is mostly peripheral, and is synthesized by chromaffin cells in the adrenal medulla. Norepinephrine and epinephrine both act on the autonomic nervous system, regulating fight-or-flight responses, as well as a number of other physiologic functions on tissues throughout the body.

In contrast to fast-acting, synaptic neurotransmitters like glutamate and GABA, dopamine and norepinephrine are more diffusely released along their axonal network in a process known as volume transmission [264, 265]. On midbrain and cortex neurons, most DAT and many dopamine receptors are located extrasynaptically [266-269], so neuronally released dopamine must diffuse through the extracellular space to bind to its receptors and to be taken back up into cells. Synaptic dopamine receptors are also present (particularly in the striatum) and are activated by precise synaptic dopamine release [267, 270]. However, following quantal dopamine release, diffusion occurs too quickly for extra-synaptic DAT uptake, resulting in extra-synaptic spillover and exposure of extra-synaptic cells to dopamine [271, 272]. The size of the region exposed to dopamine depends on complex interactions between the volume and concentration of dopamine released, the volume of extracellular fluid volume, barriers to diffusion, uptake dynamics of DAT, and the sensitivity of regional dopamine receptors [273]. HIV associated damage to dopaminergic neurons can disrupt these interactions and dysregulate dopaminergic tone [36, 119], and all drugs of abuse and many therapeutics interfere with dopamine synthesis, release, uptake, or metabolism, potentially disrupting volume transmission [274, 275]. Thus, HIV infection, particularly when combined with drugs of abuse or dopaminergic therapeutics, exposing other CNS cell types including macrophages and microglia to altered levels of dopamine.

The precise amount of catecholamines to which CNS cells are exposed depends on the catecholamine concentrations in the human CNS. These are not well defined in the human brain, but in primates and rodents, basal dopamine levels are generally reported to be between 5 – 40 nM depending on the brain region [276-278]. These can be elevated into the low micromolar range by drugs of abuse [152, 155, 279-283], which is likely to result in significant spillover into the surrounding tissue, exposing immune cells and glia to elevated dopamine. Methamphetamine can also release norepinephrine via reversal of VMAT and DAT [284], increasing levels of norepinephrine in the CNS. The basal levels of norepinephrine in the locus coeruleus and the PFC have been reported between 1-5 nM, and may be elevated by 300% during phasic stimulation [285, 286]. Amphetamine increased

basal levels of norepinephrine in the PFC and locus coeruleus up to 50 nM [287], although the significance of this finding in compared to other natural stimuli is not known. The concentration of epinephrine in the hypothalamus has been reported to be lower than 100 picomolar, and is been below the limit of detection in other brain regions [288, 289].

IV. Effects of Dopamine on HIV infection

Dopamine has long been associated with retroviral infection, as studies almost four decades ago showed dopamine-receptor antagonists such as chlorpromazine and haloperidol have a lytic effect on retroviruses and inhibit reverse transcriptase [290, 291]. More recently, Rohr and colleagues found pharmacologic dopamine increases HIV replication in Jurkat T-cells and PBMCs by promoting viral transcription through NF-κB [292, 293], and dopamine also increased HIV production in chronically infected ACH-2 T-cells [294]. Increasing dopamine availability in the CNS of SIV-infected macaques using the MAO-inhibitor selegiline and L-DOPA significantly enhanced CNS viral replication, increased microglial activation, induced vacuole formation and disrupted dendritic architecture [31, 32]. These studies indicated that dopamine, a neurotransmitter, might contribute to the progression of NeuroHIV by directly increasing infection in immune cells.

This connection is supported by studies in the SIV macaque model of HIV, where treatment with methamphetamine, which greatly enhances CNS dopamine levels [283], increased brain viral load. Methamphetamine also increased expression of the HIV co-receptor CCR5 in CNS macrophages, thereby enhancing the susceptibility of these cells to infection [295-297]. Ongoing studies in our lab have also examined the effects of dopamine exposure on HIV infection *in vitro* using primary human macrophages. These studies use dopamine concentrations (10^{-10} M – 10^{-5} M) present in the CNS during drug abuse, homeostatic and pathologic conditions [155, 276, 277, 279-282]. They show that exposing macrophages to elevated dopamine increases their susceptibility to infection. The effect on macrophages is critical to the development of NeuroHIV, as myeloid cells are thought to be the primary drivers of HIV neuropathogenesis. Primary MDM were infected with HIV_{YU2} or HIV_{BaL}, HIV strains that use the CCR5 co-receptor, which is the main co-receptor involved in the infection of macrophages. Infections in the presence of dopamine, or specific agonists for D1-like (SKF38393) and D2-like (Quinpirole) dopamine receptors show that activation of all dopamine receptor subtypes increases HIV entry into macrophages. Pretreatment with the pan-dopamine receptor antagonist flupenthixol, or the CCR5 antagonist TAK779, blocked the effects of dopamine on HIV entry, indicating that the mechanism is dependent on both CCR5 and dopamine-receptors [231, 298].

The involvement of both D1- and D2-like dopamine receptors suggests activation of a signaling pathway common to both subtypes, although canonically, different dopamine receptor subtypes mediate opposing effects. However, both subtypes of dopamine receptors can also induce Ca^{2+} release from the endoplasmic reticulum [223], which has been connected with HIV infection in a number of experiments. Interaction of HIV-gp120 with CCR5 induces Ca^{2+} mobilization via $G_{\alpha q}$ [299-302], and Ca^{2+} flux is an essential step for in HIV entry in an astrocyte model of infection [303]. Our own studies in DR1 and DR2-transfected HEK293 cells show that dopamine receptor activation potentiates Ca^{2+}

mobilization via initiated by $G_{\alpha q}$ [298]. Together, this indicates that Ca^{2+} release may be the common mechanism by which dopamine receptor activation enhances entry and suggests that PLC-mediated Ca^{2+} mobilization may be a novel therapeutic target in the prevention of HIV infection.

Although our data point to a Ca^{2+} mediated mechanism, dopamine-mediated potentiation of HIV infection act through other mechanisms, such as the NF-kB mediated effects shown in T-cells by Rohr and colleagues [292, 293]. Enhanced oxidative stress is another possible mechanism, as dopamine oxidizes to form free radicals and reactive dopamine quinones [304], and studies show HIV LTR driven reporter expression and reactivation of latent HIV in T-cells can be mediated by the interaction of reactive oxygen species (ROS) and NF-kB activation [305, 306]. The effects of dopamine in ACH-2 cells resulted from treatment with pharmacologic levels of dopamine ($6 – 10 \times 10^{-5}$ M), which increased HIV production via an oxidative mechanism. This effect was prevented by the addition of the antioxidant glutathione, indicating that the reactivation of HIV by dopamine was due to oxidative stress [294]. All these data come from T-cells, suggesting this cell type may be more vulnerable to virologic effects induced by oxidative stress, perhaps because macrophages require exposure to ROS for proper polarization and effector function [307, 308]. While our studies show 24-hour exposure to dopamine is not cytotoxic in macrophages (Gaskill et. al., unpublished results), other studies show murine bone-marrow derived macrophages (BMDM) exposed to pharmacologic dopamine (5×10^{-6}M) for 24 hours did increase expression of oxidative stress markers [309]. Taken together, these data suggest that dopamine may enhance HIV infection through several different effector pathways, and that these might differ with distinct cell types.

V. Effects of Norepinephrine on HIV infection

The few *in vitro* studies specifically examining the effects of norepinephrine on HIV infection suggest that this catecholamine can influence the HIV replication process, although the precise mechanism is unclear. Cole and colleagues found concentrations of norepinephrine (10^{-8} to 10^{-5}M) dose-dependently increased HIV infection of human PBMC stimulated with CD3/CD28 after 6 days of infection. The increase was abrogated by the β-adrenergic receptor antagonists Sotalol and Propranolol, but not the α-adrenergic-receptor antagonist Phentolamine, indicating it was mediated specifically by β-adrenergic receptors [310]. The mechanisms underlying this increase in infection were a reduction in the production of IL-10 [310] and an increase in the surface expression of CCR5 and CXCR4 [45, 50], both of which have been shown to increase HIV infection [311]. The norepinephrine mediated increases in HIV infection occur irrespective of the concentration of the infecting virus and were seen in response infection with both X4 or R5 tropic viral strains [45]. However, another study showed HIV infection of CD8-depleted, CD3/CD28 stimulated PBMC and MDM was significantly decreased by norepinephrine ($10^{-8} – 10^{-6}$ M). The decrease in HIV replication was only seen from days 9 to 18 post-infection, and unlike the experiments by Cole et. al., no impact on replication was observed during the first 8 days post-infection. Another distinction between the studies was that the mechanism by which norepinephrine decreased HIV infection was a downregulation of the HIV-1 LTR through inhibition of NF-kB [312].

To clarify these opposing findings, we examined HIV infection of MDM in the presence of the β-adrenergic receptor agonist isoproterenol, as these receptors mediated the effects on HIV infection in the majority of similar experiments. Primary MDM were inoculated with HIV in the presence the isoproterenol. In these experiments, MDM were generated from PBMC, inoculated with HIV_{YU2} or HIV_{BaL} and infection was assessed using a viral replication assay or viral entry assay as previously described [231, 298]. These experiments showed isoproterenol (10^{-9} to 10^{-6} M) did not significantly increase HIV replication at 2 – 6 days post infection (Figure 4A), nor did Isoproterenol (10^{-8} or 10^{-5} M) alter the viral entry into these cells (Figure 4B). These results indicate activation of β-adrenergic receptor does not change the entry process of the virus in macrophages, agreeing with the data from Moriuchi and colleagues. These data suggest that norepinephrine does not have a significant impact on HIV infection of MDM infection, while the data are conflicted regarding the impact on infection of CD3/CD28 stimulated PBMC, which is primarily T-cell infection. This could indicate that norepinephrine has different effects on HIV infection in distinct cell types, potentially indicating distinct signaling mechanisms by which norepinephrine mediated its effects. It is also possible that the disparity regarding the infection of activated PBMC is explained by the differences in experimental design, specifically the length of the experiments and of the norepinephrine treatments.

The data suggest that norepinephrine does not significantly impact the spread of HIV infection in myeloid cells in the CNS, although this is complicated by the study in SIV-infected macaque suggesting that CNS catecholamines can increase SIV infection [48]. The picture is still less clear in regard to peripheral infection, particularly because the *in vivo* studies suggest elevated norepinephrine exacerbates HIV pathogenesis [40, 45, 46, 204]. Irrespective of these differences, these findings demonstrate that further investigation of the impact of norepinephrine on HIV infection is needed. *In vitro* models should examine the mechanisms by which norepinephrine could enhance HIV infection in different cell types. Patient studies should investigate the correlation between norepinephrine levels, endogenous immune cell expression of adrenergic receptors and both plasma and CSF viral load. Without this research, it will be difficult to understand and effectively counteract the effects of adrenergic activation of HIV target cells on disease progression.

VI. Role of Catecholamines in HIV-associated Neuroinflammation

While it is clear that CNS catecholamines can act as immunomodulators, their effects on neuroimmunity are not well studied. Further, it remains unclear whether and how disruptions in catecholaminergic neurotransmission contribute to HIV-associated inflammation, particularly in the case of norepinephrine. However, many of the immune functions altered by activation of dopaminergic or adrenergic receptors on immune cells, such as cytokine secretion, chemotaxis and nitric oxide production, are central to the development of NeuroHIV. As myeloid cells are the primary targets for and responders to HIV infection in the CNS, the catecholaminergic effects on the inflammatory mechanisms driven by these cells are most likely to be central to HIV-associated neuropathogenesis. Thus, the interactions between the CNS catecholaminergic systems and myeloid inflammatory processes constitute a bidirectional feedback loop that could enhance the development of

NeuroHIV. Therefore, this section will focus mainly on the mechanisms by which dopamine impacts various myeloid cell functions that promote NeuroHIV.

VIa. Production of HIV-associated inflammatory mediators

Many cytokines that promote inflammation, such as IL-1β, IL-6, IL-10, IL-12, IL-18 and TNF-α, are important inflammatory regulators associated with HIV infection [1, 14, 16, 34, 313]. In particular, IL-6 and IL-1β are play an important role in HIV neuropathogenesis through immune mobilization, the activation of inflammatory cascades, and by increasing BBB permeability [313-315]. In the pre-cART era, elevated CSF IL-6 and IL-1β were often reported in individuals with HIV-dementia [316, 317], but have not been linked to cognitive impairment in the cART era [96]. Similarly, the chemokines affected by dopamine, such as CCL2, are important chemoattractants that enhance inflammation by recruiting additional immune cells [318, 319]. Elevated levels of the chemokines CCL2 and CXCL8 are found in the CSF of HIV+ individuals with neurocognitive impairment [96, 320], and CCL2 is increased soon after infection in the CNS of SIV-infected macaques [321]. The release of cytokines and chemokines is critical to the development and persistence of HIV-associated neuroinflammation, and changes in cytokine production have also been shown to alter HIV infection directly [311].

i. Dopamine—Although studies directly examining the effects of dopamine on inflammation in HIV-infected cells are rare, there are a growing number of studies demonstrating that dopamine increases the production of a number of cytokines and chemokines in myeloid cells (Table 1). Further, long term exposure of dopamine neurons to CCL2 increases extracellular dopamine release in rat striatum [322], and inflammatory cytokines have been shown to disrupt basal ganglial function [323]. And postmortem analysis of brains from patients with Parkinsons' Disease show increased levels of cytokines, including IL-1β, TNF-α and IL-6, in striatal regions [324, 325]. These data suggest that inflammation and damage in dopaminergic brain regions, such as that which occurs in HIV infection, could create a bi-directional feedback loop in which both inflammatory mediators and dopamine levels are increased over time.

Data from our laboratory support this hypothesis, showing treatment with physiologic dopamine (10^{-8} – 10^{-5}M) significantly increased production of CCL2, IL-6, CXCL8 and IL-10, and decreased TNF-α, in unstimulated or LPS-stimulated primary human monocyte derived macrophages [236]. Treatment of murine BMDMs and microglia with pharmacologic dopamine concentrations ($1.5 – 2.5 \times 10^{-4}$M) negatively regulated NLRP3 inflammasome activity, blocking nigericin-induced secretion of IL-1β and IL-18 in a D1-like dopamine receptor dependent manner. Production of IL-1β could also be inhibited in a more physiologically relevant manner through repetitive treatment with 1.5 μM of dopamine every 5 minutes for 2.5 hours [326]. Indirect increases in dopamine also modulate cytokine generation, as blocking VMAT with reserpine, thereby preventing dopamine uptake, also decreased TNF-α in the U937 myeloid cell line [327]. However, selegiline treatment, which increases CNS dopamine, increased TNF-α mRNA expression in SIV-infected macaques [32]. Disruption of striatal dopaminergic neurotransmission by expression of HIV-1 Nef in transgenic mice, potentially altering dopaminergic tone in striatum, increased CCL2

expression in microglia [328]. However, pharmacologic dopamine treatment (10^{-5} M) of murine microglial N9 cells with increased MAO activity, which should decrease dopamine levels, also increased secretion of IL-6 and IL-1β [329]. And the D2-antagonist haloperidol inhibits secretion of IL-6, IL-1β, and IL-12 in LPS-activated RAW264.7 murine macrophages, while the non-specific dopamine receptor antagonist chlorpromazine enhanced IL-10 production in mice [330, 331]. In many of these studies, inflammatory effects were driven by activity of D1-like dopamine receptors, while anti-inflammatory activities were linked to D2-like dopamine receptors, suggesting that the dopamine receptor subtypes play distinct roles in the regulation of inflammation.

ii. Norepinephrine—Numerous studies examining the effects of adrenergic receptor activation in myeloid cells (Table 2) broadly agree that both norepinephrine and epinephrine mediate predominantly anti-inflammatory effect via β-adrenergic receptors in cells stimulated with immune-activators such as LPS, Aβ or IL-18 [51, 244-246, 250, 251, 332-350]. Stimulation of α-adrenergic receptors in LPS-activated macrophages, microglia and monocytes had the opposite effect, increasing inflammatory cytokine production [249, 250, 345]. A similar pattern was found in resting or unstimulated cells treated with β-adrenergic receptor activation, which increased production of the inflammatory cytokines IL-6 [351-353], IL-1β [351, 353, 354], TNF-α [346, 351], IL-12 [346], IL-18 [355]. Interestingly, in rodent macrophages, β-adrenergic receptors activated by dopamine were also shown to decrease production of IL-12p40 and increase production of IL-10 [356]. Together, these data indicate that both α- and β-adrenergic receptor expression levels and the activation state of the cell are important to determining the effects of adrenergic neurotransmitters on cytokine production.

There is little research specifically investigating HIV-infected cells, although in HIV-infected PBMC, norepinephrine (10^{-5} M) significantly decreased production of IL-1β, IL-6, TNF-α, IL-10 and IFN-γ, with the effects on IL-10 and IFN-γ mediated through modulation of cAMP production [310]. And in HIV infected individuals with autonomic system hypo-reactivity, there was an increase in baseline TNF-α [41]. These data suggest that norepinephrine mediated activation of adrenergic receptors, particularly β-adrenergic receptors, may play an important role in the regulation of HIV-associated inflammation. This is supported by studies showing elevated stress in HIV-infected individuals, as stress increases expression of inflammatory cytokines in both the plasma and CNS via activation of β-adrenergic receptors [357]. Thus, physiologically-relevant increases in norepinephrine could exacerbate neuroinflammation during HIV, however more research is needed to determine which cells and cytokines are involved.

VIb. Changes in Chemotaxis and Transmigration

The transport of HIV into the CNS predominantly involves the transmigration of mature CD14+ CD16+ monocytes across the BBB. These mature monocytes are enriched in the blood of HIV infected individuals, and this enrichment of CD14+CD16+ cells is maintained in the presence of cART treatment [71]. These mature monocytes, particularly once they are infected, preferentially transmigrate across the blood brain barrier in response to chemoattractants such as CCL2 [67, 319]. This is a critical process in the development of

HIV-associated neurologic disease. These cells not only bring HIV into the CNS, they also contribute to neuroinflammation and differentiate into infected macrophages, which further contribute to NeuroHIV [16, 66, 67, 72]. Thus, changes in the processes by which monocytes transmigrate into the CNS, or move throughout the brain once transmigration are complete, could have a significant impact on neuropathogenesis.

i. Dopamine—Studies in the Berman lab have shown that dopamine receptor expression on monocytes changes with maturation, with mature monocytes expressing increased amounts of D1-like dopamine receptors. Dopamine increased chemokinesis in these cells, and enhanced the CCL2-mediated transmigration of these cells across a BBB model in response to dopamine and the D1-like agonist SKF38393 (10^{-6} – 5×10^{-5} M) [232, 237]. Notably, the enhancement of transmigration only applied to mature CD14+CD16+ monocytes, with transmigration of immature $Cd14^{low}$CD16+ monocytes and T-cell remaining unaffected [237]. This indicates that increased extracellular CNS dopamine could increase the accumulation of these monocytes, and the virus they are transporting, in the CNS, specifically in dopaminergic brain regions. While the effects of dopamine on macrophage chemotaxis are not clear, dopamine has been shown to stimulate microglial chemotaxis. Physiologic dopamine (10^{-7}M) significantly increases migration of human microglia relative to untreated and CCL2 stimulated chemotaxis, an effect mediated by D2-like dopamine receptors, as it was blocked by treatment with the D2-antagonist Spiperone [233]. Similar findings were reported in rodent microglia, significantly increasing chemotaxis in response to physiologic dopamine (10^{-8} – 10^{-5} M) or the D1 and D2 agonists dihydrexidine and quinpirole [51]. Dopamine may affect macrophage chemotaxis similarly, but additional research is necessary to confirm this. These studies suggest increased chemotaxis could be an important mechanism by which elevated CNS dopamine exacerbates inflammation and neurocognitive impairment in HIV-infected individuals with altered dopaminergic tone.

ii. Norepinephrine—As with cytokine production, the effects of norepinephrine on myeloid cell chemotaxis seem to be highly context and receptor-dependent. Short-term exposure to low levels of norepinephrine (10^{-10} M, 2 hrs), or isoproterenol stimulates chemotaxis of human macrophages and monocytes in a β-adrenergic receptor and cAMP dependent manner [358]. However, long term exposure of mouse BMDM to norepinephrine (10^{-6}M, 7 days) inhibited cell proliferation and migration toward CCL2 via downregulation of MHC II and CCR2, although increasing MHC II and CCR2 expression with a lower concentration of norepinephrine (10^{-8} M), and had no effect of macrophage migration [359]. In murine peritoneal macrophages, varying concentrations of norepinephrine (10^{-12} M to 10^{-3} M) induced both adherence and chemotaxis, but the effects varied with the age of the mice from which the cells were derived [360]. A second study from this group confirmed that low-level norepinephrine increased murine macrophage chemotaxis, and suggested this effect was mediated by β-adrenergic receptor activation. They also found that higher levels of norepinephrine enhanced phagocytosis [361]. In microglia, norepinephrine (10^{-7} M, 2 hrs) and isoproterenol also increase microglial migration in response to Aβ [348]. However, bath application of norepinephrine (3×10^{-5}M) to mouse cortical brain slices resulted in significant retraction of microglial processes in both resting and LPS-activated cells, with the specific adrenergic receptor subtypes involved dependent on the activation state of the

cells [362]. This suggests the presence of other cells and inflammatory factors could modulate microglial response to norepinephrine. For example, norepinephrine increases release of CCL2 from astrocytes, but inhibited CCL2 expression in microglia [363]. Astrocyte and microglia density vary in different brain regions [364, 365], so norepinephrine modulation of CCL2 expression in different cells may cause region-specific effects on chemotaxis. While the effect of norepinephrine on the chemotaxis or motility of myeloid cells has not been investigated in the context of HIV, these studies suggest that changes in the concentration of this neurotransmitter could distinctly alter myeloid migration within the HIV infected CNS, depending on the microenvironments present in specific brain regions.

VIc. Effects on Nitric Oxide Production

Nitric oxide (NO) is a key molecule in immunity and inflammation. In pathologic conditions, NO can both support or inhibit inflammation, acting in either a cytoprotective or cytotoxic capacity. Nitric oxide is produced by inducible nitric oxide synthase (iNOS or NOS2), generally after induction with immunologic or inflammatory stimuli. A variety of immune cells, particularly innate immune cells such as macrophages, both produce and respond to NO [366]. In the CNS, excessive NO production can contribute to neuronal damage and death via induction of oxidative stress [367-370]. Increases in NO production occurs during HIV infection [371, 372], with both pro- [373, 374] and anti-viral [375-377] effects. In human PBMC, HIV replication is inhibited by NO in acutely infected cells, but stimulated by NO in chronically-infected cells [378]. In the HIV-infected brain, modulation of NO the NO-arginase network in microglia reduces neuroinflammation [379], but also enhances neuroinflammation through up-regulation in response to the HIV proteins Tat and g120 [380]. The opposing effects of NO make it difficult to determine how alterations NO production would affect NeuroHIV [368].

i. Dopamine—A number of studies show dopamine-receptor activation modulates NO production (Table 1). The effects of dopamine human myeloid cells remain undetermined, but in RAW264.7 murine macrophages, pharmacologic dopamine (5×10^{-5} M) enhanced LPS-induced production of NO [381], and the D2/D3 specific agonist pramipexole and increased LPS/IFN-γ-induced secretion of NO from primary murine microglia [382]. Contrary to these findings, stimulation of primary rat microglia with pharmacologic dopamine (10^{-6}M – 10^{-5}M) for 24 hrs significantly reduced LPS mediate NO production [51], and pretreatment with higher dopamine concentrations (3×10^{-6} – 10^{-4}M) significantly reduced LPS-induced NO in BV-2 murine microglial cells [383]. The effects of dopamine were dopamine receptor dependent in the rat microglia, but not the BV-2 cells, in which they were induced by the formation of dopamine quinones. These contradictory findings suggest that dopamine impacts NO production through multiple pathways and receptors, and the specific effects on NO may reflect a concentration-dependent activation of a predominant pathway in each specific context. These data also emphasize the importance of cell origin, culture conditions, and treatment paradigm when interpreting data from various studies. Thus, further studies are needed to determine whether and how the dopaminergic changes occurring in NeuroHIV alter NO production in human myeloid cells.

ii. Norepinephrine—Adrenergic receptor activation also modulates NO production in myeloid cells (Table 2). Szelenyi and colleagues found that isoproterenol increased NO production in PMA-primed human monocytes, but decreased NO production in LPS-primed monocytes. They also found that isoproterenol decreased NO production in LPS-primed murine macrophages [346]. The β-receptor agonists isoprenaline, dobutamine, and salbutamol, as well as epinephrine, inhibited NO production in LPS-primed murine macrophages at a concentration of 10^{-7}M [344]. On the other hand, Chi and colleagues found that norepinephrine and epinephrine increased NO production in murine LPS-primed macrophages, although this study was performed in the RAW264 cell-line using a high concentration (5×10^{-6}M) of catecholamine [381]. Adrenergic receptor activation also inhibited NO production in microglia. In LPS-primed rat microglia, norepinephrine, isoproterenol, phenylephrine, dobutamine, and terbutaline reduce NO at multiple concentrations ($10^{-7} – 10^{-5}$ M) [251, 347]. In addition, norepinephrine (5×10^{-6}M), isoproterenol (2.5×10^{-7}M), and phenylephrine (7.8×10^{-6}M) all reduced NO produced in LPS-primed murine N9 microglia. These studies suggest that activation of all subtypes of adrenergic receptors can have a suppressive effect on LPS-induced NO production in most myeloid cells. However, there is still little known about how adrenergic receptor activation would impact NO production under basal conditions or during HIV infection. Further studies are needed, particularly in human macrophages to elucidate the mechanism and impact of altered NO production by norepinephrine or epinephrine.

VII. Concluding remarks

The ability to control HIV replication has greatly improved the lifespan and quality of life for infected individuals, but that transformation to a chronic disease has created a number of new issues. Among these effects is the dysregulation of catecholaminergic neurotransmission due to neuroinflammation and neurologic damage, which can result in the exposure of CNS myeloid populations to aberrant levels of catecholamines. Additionally, the effects of cART drugs on catecholaminergic systems remains undetermined, so the potential effects of these therapeutics also require further study. These alterations in catecholaminergic tone can be further exacerbated by the use of illicit drugs or legal therapeutics that modulate dopaminergic and noradrenergic neurotransmission. The effect of brain catecholamines on myeloid cell functions is highly relevant in the cART era, as the persistence of HIV within CNS monocytes and macrophages is a major obstacle to HIV-eradication and the treatment/prevention of HIV-associated neuroinflammation. This review has attempted to disentangle the bidirectional interactions between catecholamines and immune-processes implicated in HIV-infection of the CNS. The data described here suggest that elevated dopaminergic tone in the CNS may increase CNS viral load and enhance neuroinflammation through dopamine-mediated changes in myeloid inflammatory processes and susceptibility to viral infection. Elevated CNS norepinephrine may also alter HIV-infection, particularly in regard to modulation of neuroinflammation, but the direction and magnitude of these effect remain unclear due to the paucity of studies investigating the role of the adrenergic system in HIV infection. Thus, dysregulation of catecholaminergic systems through direct or indirect viral effects, elevated stress, use of illicit drugs or

catecholaminergic therapeutics, or a combination of these factors, is likely to exacerbate NeuroHIV.

However, more research is needed to determine the precise mechanisms responsible for the immunomodulatory effects of catecholamines, including the involvement of specific receptors and signaling pathways in immune cells. This is particularly true regarding the immunomodulatory effects of the adrenergic system, which remains poorly understood in the context of HIV infection. Research in this area is complicated by contradictory findings that are likely due to variations in culture conditions, treatment paradigms, and specificity of receptor agonists and antagonists. Our summary of catecholaminergic modulation of inflammatory mediators (Tables 1 and 2) reflects these contradictions. Further, they suggest that the disparate dopamine and adrenergic receptor subtypes play distinct and potentially opposing roles in inflammation. Continuing research that utilizes receptor-specific pharmacologic assays and gene-level knockdown may reveal these specific roles. Because of the differences in neurotransmission among mammals, it is important to use both *in vitro* systems involving human cells and animal models to interrogate the precise molecular mechanisms and pathways involved in this type of neuroimmune communication. Further, new technologies enabling investigation of human CNS cells, using technologies such as iPSC co-culture or multi-cell type brain organoids, provide novel platforms in which to expand these studies. Determining the effects of catecholamines on myeloid cells during HIV infection is critical to developing treatments for chronically infected individuals and may reveal important contraindications for the use of catecholaminergic therapeutics in HIV infection. Further, the proliferation of psychiatric drugs in todays' medical settings suggests that the poorly defined interactions we have described here between catecholamines and immune cells likely have larger implications for other neuroinflammatory diseases and psychiatric disorders. Therefore, understanding the interactions between catecholamine neurotransmission and immune function, particularly in myeloid cells, is critical to the creation of strategies that will ameliorate the long-term effects of catecholaminergic dysregulation in HIV-infected individuals.

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Abbreviations

BBB	blood brain barrier
BMDM	bone marrow derived macrophages
cART	combination anti-retroviral therapy
CNS	central nervous system

COMT	catechol-O-methyltransferase
CSF	cerebrospinal fluid
DAT	dopamine transporter
DBH	dopamine beta hydroxylase
DRD	dopamine receptor
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HIVE	HIV-associated encephalitis
HPA	hypothalamic-pituitary axis
HVA	homovanillic acid
iNOS	inducible nitric oxide synthase
MAO	monoamine oxidase
MDM	monocyte derived macrophages
NET	norepinephrine transporter
NO	nitric oxide
PBMC	peripheral blood mononuclear cells
PFC	prefrontal cortex
PKC	protein kinase C
PLC	phospholipase C
PMN	Polymorphonuclear neutrophil
PNMT	phenylethanolamine-N-methyltransferase
ROS	reactive oxygen species
SAM	sympathetic neuron–associated macrophages
SIV	simian immunodeficiency virus
SNP	single nucleotide polymorphism
SNpc	substantia nigra pars compacta
SNS	sympathetic nervous system
TH	tyrosine hydroxylase
VMAT2	vesicular monoamine transporter 2

VTA	ventral tegmental area

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Highlights

- Catecholamines significantly alter the development of HIV neuropathogenesis
- Catecholamines alter HIV-infection and HIV-associated immune functions
- Activation of b-adrenergic receptors does not alter HIV infection in macrophages
- Catecholamine immunomodulation could be a therapeutic target for treatment of HAND

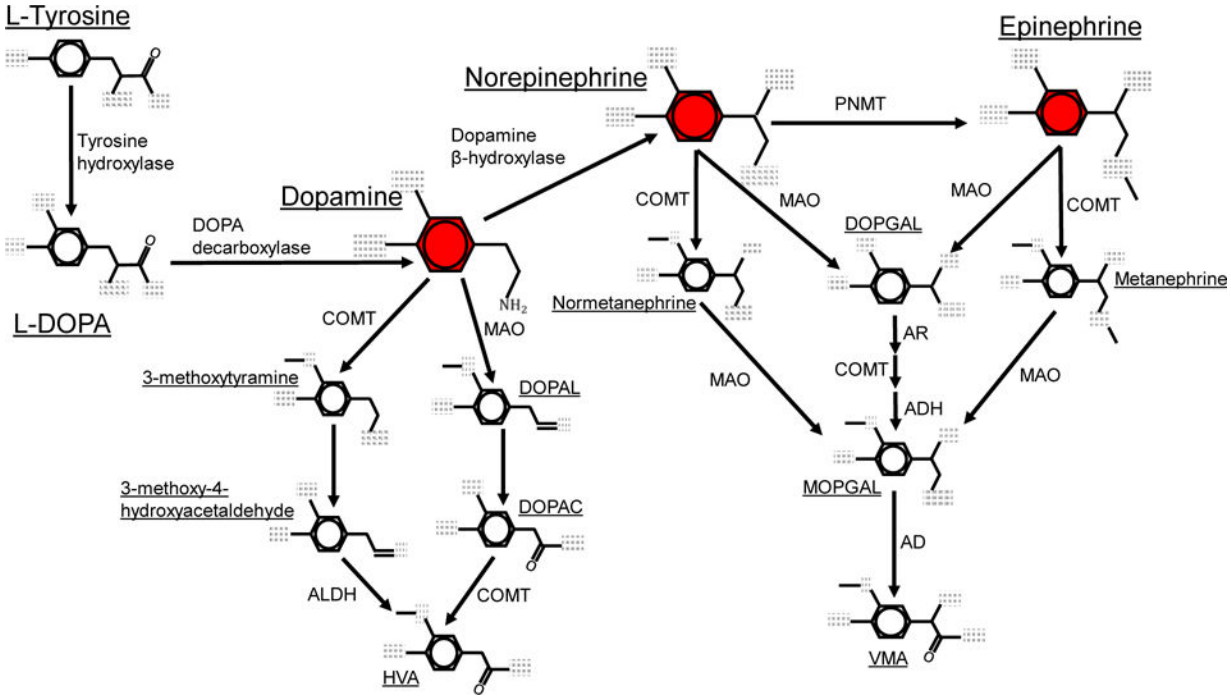

Figure 1.

Metabolic pathways for catecholamine biosynthesis and degradation. Metabolic pathways for the formation and degradation of dopamine, norepinephrine and epinephrine (shown in red) are described. Catecholamine synthesis is initiated with the hydroxylation of the amino acid tyrosine is by tyrosine hydroxylase (TH), generating L-DOPA. L-DOPA is then converted to dopamine by DOPA decarboxylase (DDC, also known as aromatic L-amino acid decarboxylase, AADC). Dopamine is hydroxylated by dopamine β-hydroxylase (DBH) to form norepinephrine, which is then converted to epinephrine by phenylethanolamine-N-methyltransferase (PNMT). The catecholamines are primarily metabolized by two enzymatic pathways with catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). COMT converts dopamine to 3-methoxytyramine, norepinephrine to normetanephrine, and epinephrine to metanephrine via meta-*O*-methylation. MAO converts dopamine to 3,4-Dihydroxyphenylacetaldehyde (DOPAL), and norepinephrine or epinephrine to 3,4-didydroxyphenylclycoaldehyde (DOPGAL) by oxidative deamination. MAO also converts 3-methoxytyramine to 3-methoxy-4-hydroxyacetaldehyde, and the metanephrines to an unstable aldehyde monohydroxyphenylglycol aldehyde (MOPGAL). MOPGAL is ultimately converted to the final product vanillyl mandelic acid (VMA) by aldehyde reductase. In the final steps of dopamine metabolism, COMT and aldehyde dehydrogenase (ALDH) convert DOPAL and 3-methoxy-4-hydroxyacetaldehyde to the final product homovanilic acid (HVA).

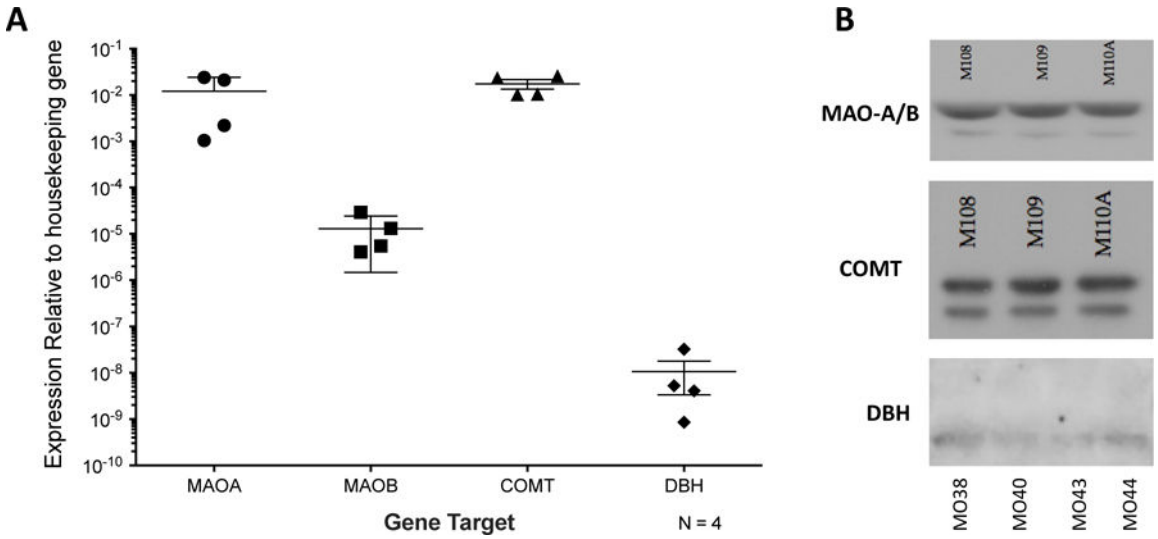

Figure 2. Human macrophages express enzymes necessary for the synthesis of norepinephrine and degradation of catecholamines

Human macrophages were generated from peripheral blood mononuclear cells that were isolated from whole blood by ficoll density centrifugation, then matured into monocyte-derived macrophages (MDM) by adherence and maturation for 6 days in 10 ng/mL M-CSF. (A) Expression of mRNA for MAO-A and MAO-B, COMT and DBH is seen in mRNA derived from MDM from 4 donors. (B) Analysis of protein lysates from MDM derived from 3 or 4 additional donors shows expression of MAO (antibody did not distinguish A and B), COMT, and DBH protein.

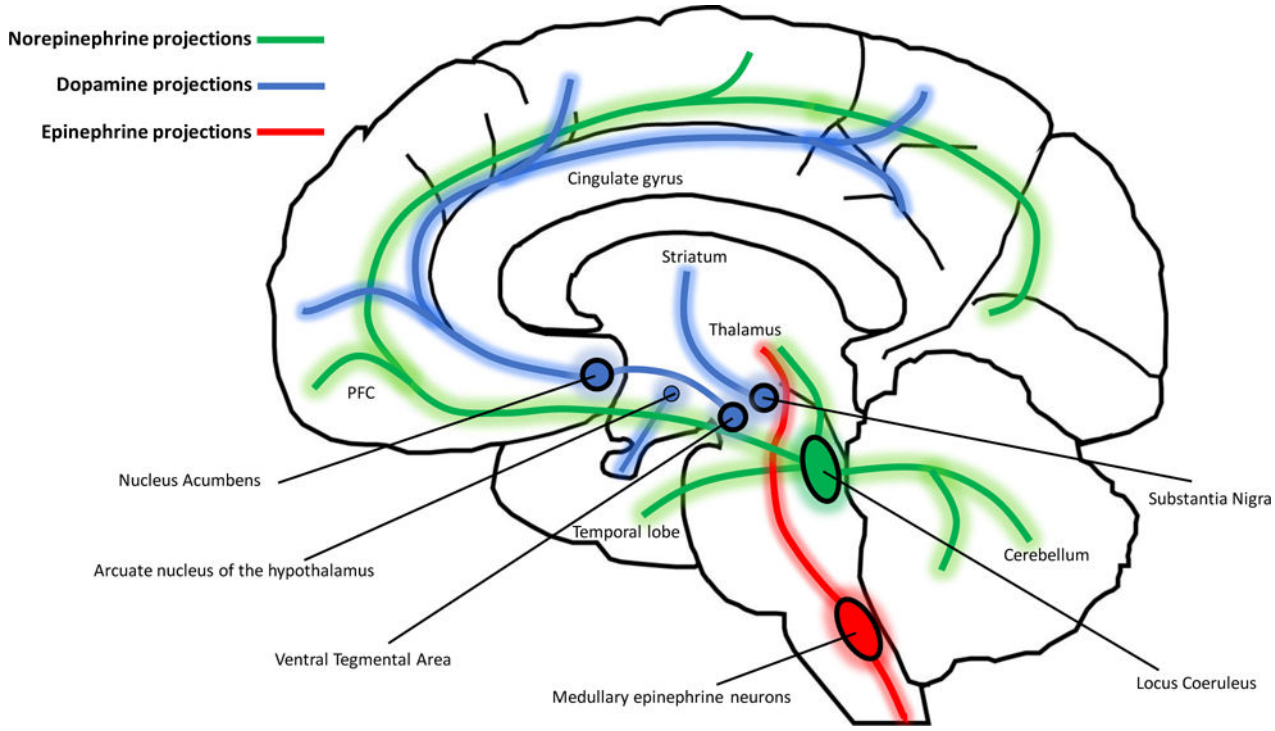

Figure 3. Anatomical location of catecholaminergic brain regions and projections

Dopamine is predominantly synthesized in midbrain nuclei that give rise to three major dopaminergic projections. The mesocortical pathway arises from the ventral tegmental area (VTA), and ascends via the median forebrain bundle to innervate prefrontal and cingulate cortices to modulate cognition, motivation, and emotional response. The VTA is also the origin of the mesolimbic pathway that projects to the nucleus acumbens, medial PFC, amygdala, hippocampus to mediate reward-based habits, emotions, and cognition. The nigrostriatal pathway ascends from the midbrain substantia nigra pars compacta (SNpc) to striatal nuclei (caudate and putamen) in the forebrain to modulate production and coordination of movement. There is an additional small group of dopamine neurons in the arcuate nucleus of the hypothalamus that project to the median eminence (via the tuberoinfundibular pathway) where dopamine is released into the hypophyseal portal system and transported to the anterior pituitary to inhibit the release of prolactin. Norepinephrine neurons from the locus coeruleus in the brainstem broadly innervate cortical and midbrain regions including the PFC, temporal lobe (hippocampus and amygdala), thalamus, hypothalamus, and cerebellum. Outside the brain, norepinephrine is released as a transmitter from postganglionic sympathetic nerve terminals near the spinal cord, and released as a hormone from the adrenal medulla into the blood stream. The role of norepinephrine is to modulate alertness and arousal (via cortical projections), and autonomic functions (via symphathetic nerves and adrenal medulla) in order to mobilize the body for action. Unlike norepinephrine and dopamine, the majority of epinephrine is synthesized in the periphery, with more than 90% of circulating epinephrine produced by chromaffin cells in the adrenal medulla. Some epinephrine may be synthesized in medullary epinephrine neurons that project to the thalamus and spinal cord, although very little is known about the function of these neurons.

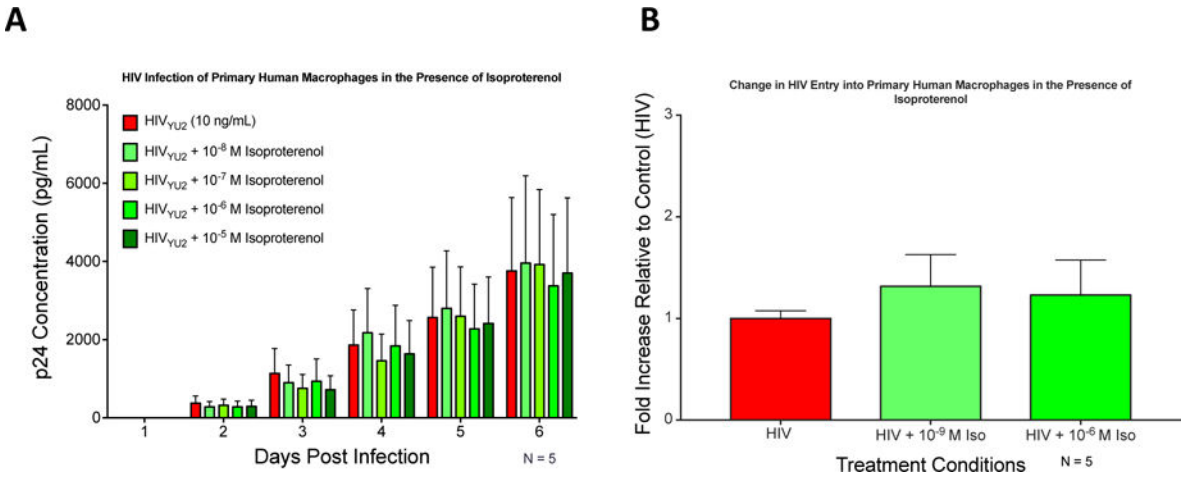

Figure 4.

Activation of β-adrenergic receptors does not increase HIV infection in human macrophages. Human macrophages were generated from peripheral blood mononuclear cells that were isolated from whole blood by ficoll density centrifugation, then matured into monocyte-derived macrophages (MDM) by adherence and maturation for 6 days in 10 ng/mL M-CSF. (A) MDM from 5 donors were infected with 10 ng•p24/mL of the brain-derived R5 virus HIV_{YU2} for 24 hours in the presence (greens) or absence (red) of the isoproterenol (β-adrenergic receptor agonist). Cells were washed after 24 hours and supernatant was collected every 24 hours for 6 days as assayed for p24•Gag as a measure of viral replication. (B) MDM from 5 donors were infected for 2.5 hours with a modified HIV_{BaL}, a lung derived R5 virus, containing an active β-lactamase enzyme, enabling visualization of entry within 9 hours of inoculation. Infections were performed in the absence (red) or presence (greens) of isoproterenol. After 2.5 hours cells were washed to remove excess virus, and incubated in CCF2-AM (ThermoFisher) for 6 hours. After 6 hours, cells were imaged and the percentage of infected cells was enumerated by fluorescent microscopy. Amount of infection displayed as fold change relative to infection with HIV alone, which was set to 1. Statistical analysis for both experiments performed using one-way repeated measures ANOVA.

Table 1

Effect of dopamine, and dopamine agonists or antagonists on cytokine & NO production

Effect of dopamine agonists/antagonists on cytokine production in myeloid cells A summary of in-vitro and in-vivo studies that have examined the effect of dopamine receptor agonists and antagonists on cytokine production in immune-cells. Haloperidol and chlorpromazine are non-specific dopamine-receptor antagonists. L-750,667 is a D4 receptor antagonist. Salsolinol and 1 BnTIQ are dopamine metabolites. Pramipexole is a D2/D3 receptor agonist.

Effect on inflammation	Dopamine agonist/antagonist	cytokine	Experimental model	citation
Macrophages				
↑	Dopamine	↑ IL-6, CCL2	Human macrophages	[236]
↑↓	Dopamine	↑ IL-8, IL-10. ↓ TNF-α	LPS-primed human macrophages	[236]
↑	Haloperidol, L750.667 (D2-like antagonist)	↓ IL-6, IL-1β, IL-12	RAW 264 murine macrophages	[330]
↓	Dopamine (effect blocked by D1 knockdown)	↓ IL-1β, IL-18	Nigericin-stimulated, LPS-primed Mouse BMDM	[326]
↑	Dopamine	↑ NO	LPS-primed RAW 264 murine macrophages	[381]
↑	Salsolinol, 1BnTIQ (dopamine metabolites)	↑ NO	RAW 264 murine macrophages	[384]
↑	Dopamine	↑ iNOS and CXCL9. ↓ IL-10, CCL22	Tumor-associated macrophages from rat glioma model	[385]
↓	dopamine (effect blocked by β antagonist)	↓ IL-12	LPS-primed mouse macrophages	[335]
↓	Dopamine (increased by treatment with reserpine)	↓ TNF-α	LPS- or PMA- treated human U937 monocytoid cells	[327]
↑↓	Dopamine (through adrenergic receptors)	↑ IL-10, ↓ IL-12p40	LPS-treated mouse peritoneal macrophages	[335]
↓	Fenoldopam (D1-like agonist)	↓ TNF-α, MIP-2	LPS-treated mouse peritoneal macrophages	[386]
↑	Chlorpromazine (Pan dopamine receptor antagonist)	↑ IL-10	staphylococcal enterotoxin-stimulated mice	[331]
↑	Selegiline/L-DOPA	↑ TNF-α mRNA	SIV infected Macaque Brain	[32]
Microglia				
↗	dopamine	↑ IL-1β, IL-6	N9 murine microglia	[329]
↑	Pramipexole (D2/D3 agonist)	↑ NO	LPS or IFN-γ primed murine microglia	[382]
↗	Dopamine (effect blocked by D1 and D2 antagonists)	↓ NO	LPS-primed murine microglia	[51]
↓	Dopamine (effect blocked by N-acetylcysteine)	↓ NO	LPS-primed BV-2 murine microglia	[383]

Table 2

Effect of adrenergic agonists and antagonists on cytokine production in myeloid cells A summary of in-vitro and in-vivo studies that have examined the effect of adrenergic receptor agonists and antagonists on cytokine production in monocytes, macrophages, and microglia. Phenylephrine is a selective α1 receptor agonist, Norepinephrine (NE) and epinephrine are non-selective α and β receptor agonists. Isoproterenol and isoprenaline are non-selective β receptor agonists. Terbutaline, salmeterol, and formoterol are selective β2 receptor agonists. Clonidine is a centrally acting α2 receptor agonist. Dobutamine is predominantly a β1 receptor agonist with weak effects on β2 and α1 receptors. Butoxamine is a selective β2 receptor antagonist. Phentolamine is a non-selective α receptor antagonist. Yohimbine is predominantly a α2 antagonist that also has moderate affinity for α1 as well as D2 and serotonin receptors. Propranolol is a nonselective β receptor antagonist.

Effect of Adrenergic agonists/antagonists on cytokine production

Effect on inflammation	Agonist/antagonist	cytokine	Experimental model	citation
Monocytes				
↑	Phenylephrine	↑ IL-1β	LPS-primed human monocytes	[249]
↑	NE, E, isoproterenol (effect blocked by β2 antagonist)	↑ IL-18, TNF-α, IFN-γ	Human PBMC	[355]
↑	NE, E, isoproterenol (effect blocked by β2 antagonist)	↑ IL-18	Human monocytes	[355]
↑	Terbutaline (effect blocked by β antagonist)	↑ IL-8	LPS primed human monocytes	[336]
↑	Isoproterenol	↑ IL-12, TNF-α, NO	PMA-primed human monocytes	[346]
↑	NE (effect blocked by β antagonist)	↓ IL-10	HIV-infected human monocytes	[310]
↓	NE, clonidine	↓ IL-6, TNF-α	LPS-primed whole blood	[244]
↓	NE (effect blocked by β antagonist)	↓ IL-6, TNF-α, IL-1β, IL-2, IL-4, IFN-γ	HIV-infected human monocytes	[310]
↓	Terbutaline, salmeterol, formoterol	↓ IL-1β	LPS-primed human monocytes	[245]
↓	NE, E (effect blocked by β2 antagonist)	↓ TNF-α	LPS-primed human monocytes	[334]
↓	E, isoproterenol (effect blocked by β2 but not α antagonist)	↓ MIP-1	LPS-primed human monocytes	[349]
↓	Dobutamine, salbutamol	↓ MIP-1, IL-8	LPS-primed human monocytes	[350]
↓	Dobutamine	↓ CCL2	LPS-primed human monocytes	[337]
↓	Salbutamol, butoxamine, terbutaline	↓ IL-18, IL-12	LPS-primed human monocytes	[339]
↓	NE, E, isoproterenol, salbutamol, terbutaline	↓ TNF-α, IL-12, IFN-γ	IL-18-primed human monocytes	[341]
↓	Isoproterenol	↓ TNF-α, IL-12, NO	LPS-primed human monocytes	[346]
↓	NE, E, terbutaline	↑ IL-10, IL-4. ↓ IFN-γ	tetanus-primed human monocytes	[332]
↓	Terbutaline	↑ IL-10, ↓ TNF-α	LPS primed U937 human monocytes	[336]
Macrophages				
↑	NE	↑ TNF-α	LPS-primed mouse macrophages	[359]
↑	Phenylephrine	↑ IL-1β	LPS-primed human macrophages	[249]

Effect on inflammation	Agonist/antagonist	cytokine	Experimental model	citation
↑	Phentolamine, yohimbine	↓ IL-1β	LPS-primed mouse macrophages	[250]
↑	NE (effect blocked by β antagonist)	↑ IL-6	U937 human macrophages	[352]
↑	NE, E	↑ NO	LPS-primed RAW 264 murine macrophages	[381]
↑	Salbutamol	↑ IL-1β, IL-6	RAW 264 murine macrophages	[353]
↑	Isoproterenol	↑ TNF-α, IL-12, NO	PMA-primed mouse macrophages	[346]
↓	E, isoprenaline, dobutamine, salbutamol	↓ NO	LPS-primed mouse macrophages	[344]
↓	Propranolol	↑ IL-1β	LPS-primed mouse macrophages	[250]
↓	Isoproterenol (effect blocked by β antagonist)	↓ TNF-α	LPS-primed mouse macrophages	[345]
↓	NE, E, formoterol, salbutamol	↓ IL-27	LPS-primed mouse macrophages	[340]
↓	NE, E, formoterol (effect blocked by β2 antagonist)	↓ TNF-α, IL-8. ↑ IL-10	LPS-primed porcine macrophages	[342]
↓	Dopamine (effect blocked by β antagonist)	↓ IL-12	LPS-primed mouse macrophages	[335]
↓	Clenbuterol	↓ TNF-α, IL-6. ↑ IL-10	LPS-primed PMA-differentiated U937 human macrophages	[246]
↓	Isoproterenol	↓ TNF-α, IL-12, NO	LPS-primed mouse macrophages	[346]
Microglia				
↑	Isoproterenol (effect blocked by β antagonists)	↑ IL-1β	Rat microglia	[354]
↑	Isoproterenol	↑ IL-6, IL-1β, ↓TNF-α	Rat microglia	[351]
↑	Propranolol	↓ IL-6, IL-1β, ↓TNF-α	Rat microglia isolated after surgical trauma	[351]
↓	NE, isoproterenol	↓ TNF-α, CCL2	Aβ stimulated mouse microglia	[348]
↓	NE, isoproterenol	↓ NO	LPS-primed rat microglia	[347]
↓	NE, epi, isoproterenol, phenylephrine	↓ NO	LPS-primed N9 murine microglia	[333]
↓	NE	↓ TNF-α, IL-6	LPS-primed mouse microglia	[51]
↓	NE, phenylephrine, dobutamine, terbutaline	↓ TNF-α, NO	LPS-primed rat microglia	[251]
↓	dobutamine, terbutaline	↓ TNF-α, CCL2, IL-6	LPS-primed microglia in mouse hippocampal slices	[338]
↑	Isoproterenol (effect blocked by β antagonists)	↑ IL-1β	Rat microglia	[354]
↑	*Isoproterenol*	↑ *IL-6, IL-1β, TNF-α*	*Rat microglia*	[351]