

Heme Oxygenase-1 Dysregulation in the Brain: Implications for HIV-Associated Neurocognitive Disorders

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Abstract: Heme oxygenase-1 (HO-1) is a highly inducible and ubiquitous cellular enzyme that subserves cytoprotective responses to toxic insults, including inflammation and oxidative stress. In neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis, HO-1 expression is increased, presumably reflecting an endogenous neuroprotective response against ongoing cellular injury. In contrast, we have found that in human immunodeficiency virus (HIV) infection of the brain, which is also associated with inflammation, oxidative stress and neurodegeneration, HO-1 expression is decreased, likely reflecting a unique role for HO-1 deficiency in neurodegeneration pathways activated by HIV infection. We have also shown that HO-1 expression is significantly suppressed by HIV replication in cultured macrophages which represent the primary cellular reservoir for HIV in the brain. HO-1 deficiency is associated with release of neurotoxic levels of glutamate from both HIV-infected and immune-activated macrophages; this glutamate-mediated neurotoxicity is suppressed by pharmacological induction of HO-1 expression in the macrophages. Thus, HO-1 induction could be a therapeutic strategy for neuroprotection against HIV infection and other neuroinflammatory brain diseases. Here, we review various stimuli and signaling pathways regulating HO-1 expression in macrophages, which could promote neuronal survival through HO-1-modulation of endogenous antioxidant and immune modulatory pathways, thus limiting the oxidative stress that can promote HIV disease progression in the CNS. The use of pharmacological inducers of endogenous HO-1 expression as potential adjunctive neuroprotective therapeutics in HIV infection is also discussed.

Keywords: Dimethyl fumarate, heme oxygenase, HIV associated neurocognitive disorders, HO-1, oxidative stress, neuroinflammation.

OXIDATIVE STRESS IN HIV INFECTION

Evidence for a role of oxidative stress in the pathogenesis of HIV infection in both systemic and central nervous system (CNS) compartments has consistently been demonstrated in HIV infected individuals. HIV infection can induce systemic oxidative stress [1-4] through both chronic immune activation [5-7] and direct effects of HIV proteins [8-10]. Individuals infected with HIV express diminished levels of glutathione – a potent endogenous antioxidant – in plasma and peripheral blood mononuclear cells (PBMCs) generally, and specifically in lymphocytes and monocytes [11-13]. Infected individuals also express elevated serum levels of the lipid peroxidation products malondialdehyde and hydroperoxide [14-16]. HIV infected cells demonstrate reduced levels of thioredoxin (a thiol antioxidant) [17], and the HIV proteins gp120 [8, 18-22], Vpr [10, 23], and Tat [9, 18] can directly induce cellular oxidative stress. Oxidative stress within infected cells can promote HIV replication through nuclear factor-kappa B (NF- κ B)-driven transcriptional regulation [24-26] and inflammatory cytokine release [24, 27-31], thereby perpetuating systemic immune activation and disease progression. In clinical studies, markers for increased oxidative stress in plasma and

circulating CD4+ T-lymphocytes correlate with disease progression in HIV infected individuals [32-34].

HIV infection of the brain, which likely occurs through infiltration of infected immune cells such as monocytes and T lymphocytes, also induces oxidative stress within the CNS [5, 6, 27, 35-37]. HIV proteins such as gp120 [8, 18, 38], Vpr [10, 39], and Tat [9, 18, 30] have been implicated in the direct induction of oxidative stress in several CNS cell types. In macrophages, the primary CNS reservoir for HIV replication, oxidative stress drives neurotoxin production [28, 37, 40-44], and markers of oxidative stress correlate with neurocognitive impairment [27, 43, 45] in HIV-infected individuals. Thus, the mechanisms and pathways by which HIV infection drives immune activation and its associated oxidative stress could be the targets for attenuating disease progression in both systemic and CNS compartments.

Although HIV does not infect neurons, HIV infection can result in a clinical syndrome of neurological and behavioral deficits known as HIV-associated neurocognitive disorders (HAND), which are pathologically associated with neuronal injury and neuronal loss. Chronic HIV infection in the CNS drives immune activation of resident macrophages and microglia, pervasive reactive astrocytosis, perivascular inflammation and infiltration of monocytic cells [46], which can result in HIV-encephalitis (HIVE), especially in those not receiving combination antiretroviral therapy (cART)[47]. Although the morbidity and mortality of HIV infection and the severity of neurocognitive impairment and associated neuroinflammation in HAND have significantly decreased

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since the introduction of cART in 1996 [48-53], neuroinflammation persists at or above that observed in the pre-ART era [48, 50, 51, 53, 54], and systemic and CNS markers of activation of macrophages correlate with neurocognitive impairment in chronic HIV infection [55-63], even when HIV levels are controlled with cART [64-68]. Interestingly, the clinical severity of HAND correlates more with monocyte infiltration and monocyte-derived macrophages (MDM) and microglia activation than with CNS viral antigen load or number of HIV-infected cells in the brain [68-72].

MACROPHAGES AND MICROGLIA AS MEDIATORS OF HAND NEUROPATHOGENESIS

While systemic effects of HIV infection are likely driven by HIV infection of CD4⁺ T-lymphocytes, the CNS effects of infection are predominantly driven by HIV infection of macrophages and microglia. Within the CNS productive HIV infection, i.e. infection resulting in the production and release of new infectious virions, occurs in perivascular macrophages and microglia, while HIV infection in astrocytes is non-productive [73-76]. Monocytes originate from the bone marrow, travel through the vasculature, and can differentiate into dendritic cells (DCs) in the periphery, or given the appropriate chemotaxis signal can transverse across the endothelial cell barrier into underlying end-organs; DCs do not cross this vascular barrier as readily as monocytes. After or during transmigration, monocytes differentiate into perivascular macrophages, often referred to as monocyte-derived macrophages (MDM). Monocytes express the receptor CD14, and all cells of the monocyte-lineage – e.g. MDM and DC – continue to express CD14 after differentiation. Migration of HIV-infected monocytes across the blood-brain-barrier (BBB) is believed to be the primary source of HIV entry into the CNS. However, it should be noted that other possible routes of HIV entry into the brain include transmigration of HIV-infected T lymphocytes from the blood into CNS tissue or parenchyma [77-79], and infection of or transcytosis through brain microvascular endothelial cells that comprise the BBB [80-86], although there is limited pathological evidence for these routes of entry. See Fig. (1) for a schematic model of HIV neuropathogenesis.

It is still uncertain how and when HIV enters the CNS, and two different models have been proposed: the “Trojan horse” and “late invasion” models. In the “Trojan horse” model, the virus is carried across the BBB early during the course of infection by infiltrating macrophages, and only later during infection, the virus is activated to replicate, recruiting additional monocyte/macrophages into the CNS *via* cytokine and chemokine signaling, and increased BBB permeability. In the “late invasion” model, chronic immune dysregulation in the periphery leads to an expansion of activated monocyte population from bone marrow that is highly invasive into the CNS and other end-organs [87].

MACROPHAGE NEUROTOXIN PRODUCTION

The neuropathology of HAND is described as decreased CNS neuronal synaptic and dendritic density [70, 88, 89], neuronal cell death [72, 90-92], and altered neuronal cell

functioning [93-101], each of which has been linked to persistent inflammation and oxidative stress. These neurotoxic effects likely result from effects of soluble factors released from HIV-infected monocyte-derived macrophages (HIV-MDM) and immune-activated MDM, microglia and astrocytes [102-105]. Many studies have implicated excitotoxic activity through N-methyl-D-aspartate-receptor (NMDAR) over-activation [106-108]. The other neurotoxins released from HIV-MDM or microglia are glutamate [109], quinolinic acid [110, 111], NTox [112], platelet activating factor [113], TNF α [114], and the HIV proteins gp120 [115, 116] and Tat [108, 117] and others. Analysis of cerebrospinal fluid (CSF) from HIV-infected individuals demonstrated increased levels of glutamate [118-120], quinolinic acid [111, 121], platelet activation factor [113], TNF α [108, 114], and other excitotoxins, which correlate with increased severity of HAND and with neuroinflammation. Several of these neurotoxins also alter astrocyte function, in particular glutamate homeostasis.

HEME OXYGENASE-1 AND HIV CNS INFECTION

Despite the multi-faceted nature of CNS damage by HIV, there may be an innate host response to combat the pathological effects of neuroinflammation and oxidative stress. Heme oxygenase-1 (HO-1, alternatively referred to as heat shock protein-32, HSP32), initially identified as a phase II detoxifying enzyme that degrades free heme, has been shown to have potent anti-oxidant qualities and to be highly inducible in response to numerous toxic insults, including heat-shock [122-127], ultraviolet radiation [128], ischemia and/or hypoxia [129-131] or hyperoxia [132], heavy metals [130, 133, 134] and exposure to reactive oxygen species (ROS) [126, 128, 135-141]. To counter the neuroinflammation and oxidative stress, a normal cellular response is acute induction of HO-1 expression, which generates the potent antioxidants bilirubin and biliverdin, as well as carbon monoxide, which has also pro-survival effects [142, 143]. However, whether this response occurs within the CNS during HIV infection has not been reported.

HO-1 is highly expressed in CNS cells, primarily astrocytes, macrophages and microglia, particularly during brain injury in several disease states, including Alzheimer’s disease [144-146], Parkinson’s disease [147-149], Pick disease [150], Huntington’s disease [151] and multiple sclerosis [152, 153] (for more reviews on neurodegenerative disorders: [154-157]). Recent work from our lab has demonstrated a *deficiency* of HO-1 expression in the brains of individuals with HAND with and without encephalitis (Gill *et al. in revision*), and in HIV-MDM *in vitro* [158], which suggests a possible role for HO-1 deficiency in the neuropathogenesis of HAND.

HEME, HEMOGLOBIN SCAVENGING AND HEME OXYGENASE-1 INDUCTION

As the name suggests, a primary function of heme oxygenase is to metabolize heme. Heme is a porphyrin molecule with a bound iron (Fe⁺⁺) ion, and is a prosthetic group used by hemoglobin and myoglobin proteins to

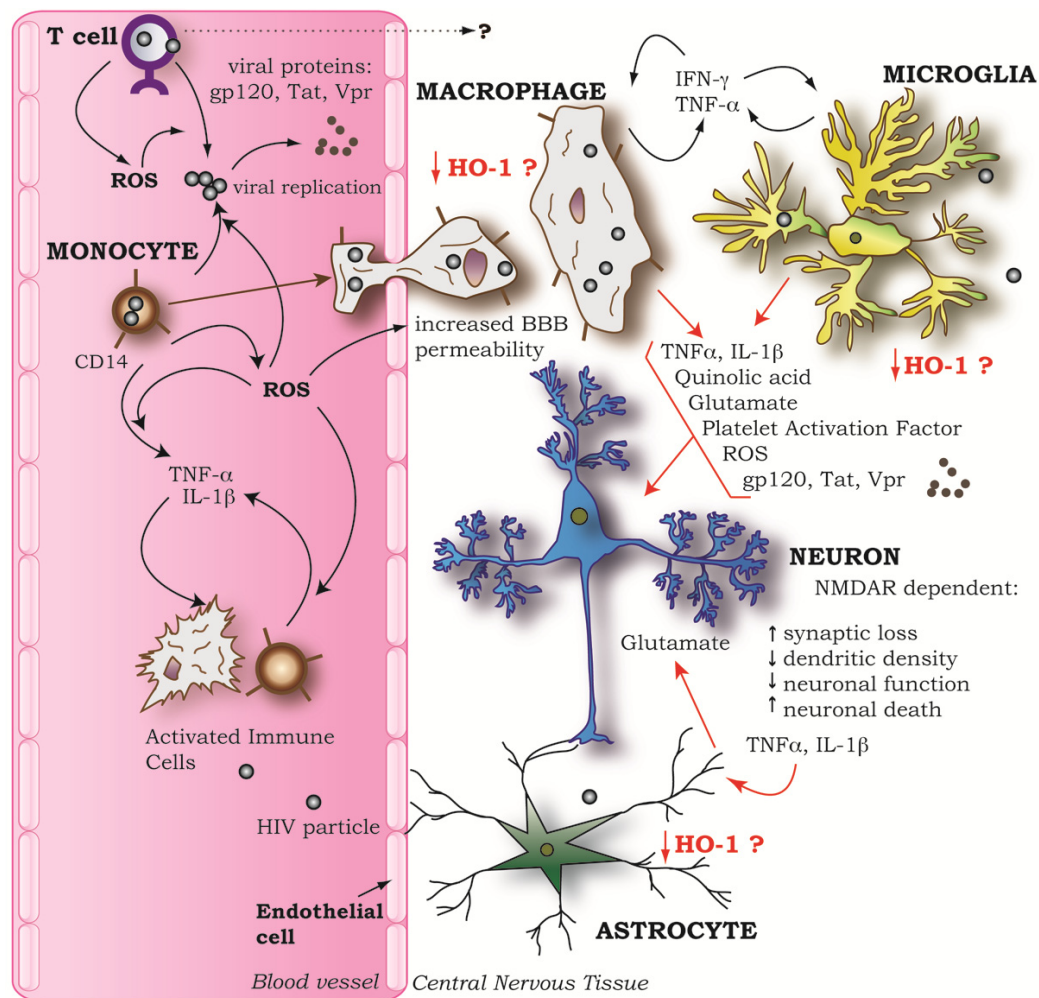


Fig. (1). Model of HIV Neuropathogenesis. HIV infected immune cells, including CD4+ T cells and CD14+ monocytes, circulate through the blood and produce reactive oxygen species (ROS), which can further enhance viral replication and release. Infected or activated immune cells can also release the pro-inflammatory cytokines, TNF- α and IL-1 β , which ROS can exacerbate. HIV proteins – gp120, Tat, and Vpr – may also be released and induce toxicity independently of infectious virions. ROS contribute to increased blood brain barrier (BBB) permeability, which can allow for increased entry of infected immune cells (e.g. monocytes) from the blood into central nervous tissue; infected T lymphocytes may also be a source of virus entry into the CNS. As monocytes enter the nervous tissue they differentiate into macrophages, and release IFN- γ in addition to TNF- α . HIV may replicate in macrophages and may be transmitted to microglia, which in turn can further replicate and transmit HIV. Infected or immune-activated microglia or macrophages can produce IFN- γ and TNF- α in a positive feedback loop, and can release a host of neurotoxic factors. Most neurotoxicity is initially limited to synaptic loss and decrease in dendritic density that is dependent on the NMDA-type glutamate receptor. This leads to eventual loss of neuronal function and finally neuronal death. HIV can infect but not productively replicate in astrocytes. Activated astrocytes have abnormal glutamate metabolism, leading to excess glutamate release and excitotoxicity. TNF- α and IL-1 β stimulation of astrocytes can further increase glutamate release. Astrocytes, microglia and macrophages are potent inducers of heme oxygenase-1 (HO-1), which is downregulated in infected macrophages and in HIV-infected brains, and thus may also contribute to neuropathogenesis of HIV infection; neurons demonstrate very limited expression of HO-1. Red arrows indicate potential neurotoxins or direct neurotoxic pathways.

transport oxygen (O_2) by the binding of O_2 to Fe^{++} . Erythrocytes also known as red blood cells (RBCs) are abundant with heme due to their abundance in hemoglobin, as the primary carriers of oxygen to tissues not capable of direct gas exchange with the external environment. Macrophage scavenging and phagocytosis of hemoglobin-containing senescent erythrocytes (but not erythrocytes without hemoglobin) induce HO-1 expression [136, 159]. Indeed, monocytes/macrophages appear to function as the major scavenger of free hemoglobin in the vasculature. Monocytes/macrophages express the membrane protein

CD163, which binds to free hemoglobin [160-162] and induces HO-1 expression [163-165]. HO-1 expression is essential for monocytes/macrophages viability during erythrophagocytosis as such cells deficient in HO-1 (HO-1 $-/-$) die due to this activity [166].

Free heme or hemin also induces HO-1 in monocytes/macrophages [167-169]. Macrophages also express CD91/lipoprotein receptor related protein (LRP), which scavenges free hemoglobin and induces HO-1 transcription upon binding [170]. Interestingly, CD91/LRP is expressed in several other cell types, such as neurons,

although it is unclear if it also functions to scavenge hemoglobin or induce HO-1 in neurons [170]. This induction of HO-1 in monocytes/macrophages through hemoglobin/heme binding, however, can be abrogated by other cellular cues. In particular, binding of the platelet derived CXCL4 inhibits CD163 expression and thus also HO-1 induction [171]. Exposure to lipopolysaccharide (LPS) can also inhibit CD163 expression and HO-1 induction in monocytes [162]. Moreover, oxidized hemoglobin induces a structural alteration that does not allow binding of CD163 to signal downstream to increase HO-1 expression [172]. Thus HIV may indirectly reduce HO-1 in monocytes/macrophages due to the increased levels of ROS and oxidative damage in HIV infection.

HO-1 enzymatic breakdown of heme yields bilirubin, which is further converted to biliverdin, both of which are potent free radical scavengers. Thus, macrophages can induce HO-1 to counteract the high levels of ROS they produce during phagocytosis, including phagocytosis of parasites, which are released in order to better destroy the engulfed material [173-175]. Indeed, exposure to external ROS can induce HO-1 in monocytes/macrophages [139, 176, 177]. HO-1 may also induce the production of glutathione, another potent endogenous antioxidant [173, 178], and depletion of glutathione may itself trigger HO-1 induction [179].

INFECTIOUS AGENTS AND HEME OXYGENASE-1: BENEFICIAL AND INJURIOUS RESPONSES

In addition to heme metabolism and oxidative stress, monocytes/macrophages increase HO-1 expression in response to viral and bacterial agents as well. Several studies have shown robust induction of HO-1 in monocytes/macrophages following exposure to LPS, typically found in Gram-negative bacteria [180-185]. Also, in at least one study, HO-1 is found to be induced by and protective against non-tuberculous mycobacterial infection [186]. HO-1 is also induced during tuberculosis infection, however it is unclear whether this promotes or reduces infection [187]. Herpes simplex virus-1 (HSV-1) encephalitis induces a strong HO-1 response in macrophages in the brain [188, 189]; and infection of neurotropic Borna disease virus (BSV) in the brain leads to sustained HO-1 induction in activated microglia, reactive astrocytes and mononuclear infiltrates for up to 4 weeks post-infection, presumably as a neuroprotective response [190].

The macrophage production of HO-1 during other parasitic infections might subservise both beneficial and injurious responses. As monocytes/macrophages express HO-1 to protect against the ROS they release to kill engulfed pathogens, induction of HO-1 helps to promote monocytes/macrophages survival and maintain degradative function. However, certain parasites have found ways to exploit the protective effects of HO-1 expression in monocytes/macrophages. For example, *Leishmania chagasi* promastigote infection in macrophages, persists longer in macrophages that express HO-1 [191], and the ability of HO-1 to reduce superoxide production is thought to aid in *Leishmania Mexicana pifano* amastigote infection [174]. However, drugs that are successful in controlling *Leishmania*

donovani appear to do so by increasing HO-1 expression in THP-1 monocytic lines [192].

In contrast, higher HO-1 expression is associated with increased susceptibility to malaria (*Plasmodium falciparum*) infection [193-196]. This may be due to the heme overload from malaria-induced hemolysis, from which increased HO-1 activity would lead to an overload of free iron [197]. HO-1 expression is high in the malaria-infected brain, monocytic cells and microglia that surround the classic malaria granulomas (Durck's granulomas), [198]; however, whether this is a beneficial or injurious response to bleeding and free hemoglobin rather than a direct response to the malaria pathogen is unknown, as other reports have found that HO-1 expression can be protective against the disease [199, 200].

INJURY-INDUCED HEME OXYGENASE-1 EXPRESSION IN THE BRAIN

Although neurons appear to have little to no HO-1 inducibility within the brain, some neurons in the spinal cord peripheral nervous system (PNS) show increased HO-1 expression in response to injury [201-203]. Some reports indicate that cortical neurons can express HO-1, if only for a few hours [204-207]. In contrast, HO-1 is robustly expressed in astrocytes, macrophages, microglia, and oligodendrocytes in response to injury [201, 208, 209], including hypoxia/ischemia [204, 207, 210].

Perivascular macrophages within the brain can express high levels of immunoreactive HO-1 during injury. This is especially true where there is hemorrhage [201, 205, 211, 212]. In particular, CD163+ macrophages appear to be primary inducers of HO-1, at least in response to traumatic brain injury (TBI) [213, 214]. Increased permeability of the BBB is also sufficient to induce HO-1 expression in astrocytes and macrophages/microglia [215]. There is prolonged expression of HO-1 in microglia and macrophages, with reports of up to 42 days [203], 5 months [206], or 6 months after the initial injury [216].

FUNCTIONAL CONSEQUENCES OF INDUCED BRAIN HO-1 EXPRESSION

In most reports, the increased expression of HO-1 is thought to be neuroprotective given the many beneficial cellular effects of HO-1 [157]. However, there is evidence that in some cases HO-1 induction may exacerbate injury, and therapeutic interventions that reduce HO-1 in glia have been proposed for certain neurodegenerative diseases [156]. For example, Wang & Doré [212] reported that HO-1 knock-out mice had less brain injury due to intracerebral hemorrhage than their wild-type counterparts, along with overall reduction in leukocyte infiltration, microglial/macrophage activation, and free radical levels. Also, macrophage cell lines (RAW 264.7) that express the Apo-ε4 allele – a known genetic risk factor for Alzheimer's disease – express higher levels of HO-1 than cells expressing the Apo-ε3 allele [217].

There are some interesting reports of brain injury surprisingly causing damage in other organ systems. For example, increased macrophage HO-1 expression in either the kidney or lung is seen in brain death during kidney

transplantation [218], and acute lung injury following TBI [219]. This suggests that either there is a humoral signal released within the brain (e.g. monocytes/macrophages, astrocytes, microglia, neurons) that activates macrophages in the periphery, or that macrophages activated in the injured brain are able to migrate out of the CNS into the periphery and into other organs. These findings may suggest that constitutive HO-1 expression in non-injured or healthy tissue may cause tissue damage, and may be the reason HO-1 is expressed as an inducible rather than a constitutive protein.

There are numerous examples of beneficial effects of HO-1 induction in the CNS. Induction of HO-1 in astrocytes is reported to reduce microglial activation, ROS levels and leukocyte infiltration in a mouse model of HSV-1 encephalitis [189], and HO-1 is briefly induced in astrocytes following excitotoxicity [220]. In addition, some metabolites of the kynurenine pathway expressed in activated macrophages and microglia - hydroxyanthranilic acid (3-HAA) and 3-hydroxykynurenine (3-HK) – inhibit cytokine release and cytokine-induced neuronal death, which may be due to the ability of 3-HAA to induce HO-1 in astrocytes [221]. HO-1 expression in macrophages/microglia is particularly beneficial in the spinal cord, as shown in experimental autoimmune encephalitis mouse models [222] and spinal cord injury [223]. Furthermore, HO-2 may be neuroprotective, as neuronal expression of HO-2 is increased in response to hypoxia-ischemia [207], and HO-2 knock-out mice show increased brain swelling, neuronal death, leukocyte infiltration, free radicals and activation of astrocytes and microglia/macrophages due to intracerebral hemorrhage in comparison with wild-type mice with intracerebral hemorrhage [224].

SIGNALING PATHWAYS OF HEME OXYGENASE-1 EXPRESSION

The canonical mechanism of HO-1 induction is related to the antioxidant response (AR) pathway mediated by the master transcriptional regulator, nuclear factor erythroid-2 related factor 2 (Nrf2). Nrf2 is normally sequestered in the cytosol by its binding partner, Keap1, which helps target Nrf2 for degradation [225]. However, upon exposure to oxidative stress, Keap1 is degraded, which allows Nrf2 to translocate to the nucleus and activate transcription of many genes that function to protect and repair damage due to oxidative stress [226]. However, the specific signaling pathway(s) of Nrf2 activation are still unclear, as several regulatory kinases have been implicated, which may vary due to the type of stimulus the cell detects.

There appear to be several signaling pathways that can lead to HO-1 expression. LPS is commonly used to induce HO-1 expression; and as the major detector of LPS, Toll-like receptor-4 (TLR4) would be predicted to mediate HO-1 induction. Indeed, several studies have shown TLR4-mediated HO-1 induction, particularly in macrophages [182, 184, 227] and MyD88-dependent signaling of HO-1 expression [228]. There appears to be a negative feedback loop whereby HO-1 induction leads to decreased TLR4 expression [229, 230], or inhibits the signaling properties of TLR4 [231, 232]. The alpha7 nicotinic acetylcholine receptor [233] and the beta adrenergic receptor in RAW 264.7 macrophage cell lines [234] are also reported to

initiate HO-1 expression, either through protein kinase C (PKC) or protein kinase A (PKA), respectively. Some reports state the HO-1 expression is signaled *via* PKC activity [183, 235], while others report extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK)-mediated induction [236, 237], and perhaps activation of both PKC and ERK [238]. ERK may also regulate HO-1 production at the translational level rather than at the transcriptional level [239]. Other major kinases have also been shown to function in HO-1 induction, including p38 MAPK [231, 240-246] and c-Jun N-terminal kinase (JNK) 1/2 [247, 248].

While many reports show or suggest Nrf2-dependent binding to the antioxidant response element (ARE) in the HO-1 promoter as the major inducer of HO-1 expression [249], there is evidence for Nrf2 independent HO-1 induction. The transcription factor activator protein-1 (AP-1) binds to at least 2 different enhancer elements (4kb and 6kb upstream) in the HO-1 promoter, and such binding is necessary for LPS and hyperoxia-mediated induction of HO-1 [180, 250, 251]. In ethanol induction of HO-1, Nrf2 was explicitly determined to be nonfunctional in HO-1 expression while AP-1 was necessary [248]. The HO-1 promoter also contains a cAMP-response element (CRE) approximately 650 bp upstream of the transcription start site, which is necessary for HO-1 induction [252]. AP-1 can bind this region, as well as the transcription factor CREB (cAMP-response element binding) protein, known to be regulated by PKA [253, 254]. The HO-1 promoter also contains binding sites for nuclear factor-kappa B (NF-κB) 156 bp and 370 bp upstream from the transcription start site [181, 255-257]. It is also reported that HO-1 leads to reduced NF-κB p65/Rel A levels [258, 259], which may suggest a negative feedback mechanism of NF-κB.

CYTOKINE AND HEME OXYGENASE-1 SIGNALING AND FEEDBACK

Apart from the primary enzymatic function of heme catabolism, and bilirubin and carbon monoxide production, all of which have cytoprotective effects, increased HO-1 expression also correlates with altered expression of several cytokines. In many reports, HO-1 appears to promote the expression of anti-inflammatory cytokines and dampen the expression of pro-inflammatory cytokines. Interleukin-10 (IL-10) is a classic anti-inflammatory cytokine, and several reports have shown that induction of HO-1 directly leads to increased IL-10 production [260-265]. Furthermore, HO-1 expression inhibits expression of the prototypical pro-inflammatory cytokine tumor necrosis factor-alpha (TNFα) [230, 263, 264, 266, 267]. Induction of HO-1 also reduces expression of other pro-inflammatory cytokines such as IL-1β [267, 268], IL-6 [175, 261, 269], IL-33 [230] and monocyte chemoattractant protein-1 (MCP-1) [175, 259, 267, 270, 271].

At the same time, these HO-1 regulated cytokines may feedback to regulate HO-1 expression itself. In macrophages, IL-6 appears to increase HO-1 [272], while TNFα treatment in CD14+ cells leads to decreased HO-1 expression [273]. Several reports show that exposure to IL-10 directly induces HO-1 [163, 272, 274-276]. Furthermore, some evidence suggests that IL-10-induced inhibition of TNFα expression

is mediated by HO-1 expression [241]. In microglia, IL-10 and HO-1 appear to be co-induced by the anti-inflammatory cytokine, IL-34 [277], further implicating a synergistic association between IL-10 and HO-1.

Although most reports point to the anti-inflammatory properties of HO-1, there are a few studies to the contrary. In RAW 264.7 macrophages, HO-1 inhibition is associated with decreased TNF α expression [268]; however the reverse experiment of HO-1 induction has not been performed to confirm this conclusion. It is also reported that HO-1 induces MCP-1 expression, although contradictory evidence has been published. In one study, genetic deficiency of HO-1 in macrophages (and other myeloid cells) resulted in reduced MCP-1 expression upon viral infection or TLR3 and TLR4 stimulation [222]; however given the range of other cytokines and downstream transcription processes HO-1 regulates, it is difficult to state a direct effect of HO-1 expression leading to increased MCP-1 production. Another study with epithelial cells also reported increased MCP-1 with increased HO-1, using hemin as an inducer of HO-1 [278]; while hemin is a strong inducer of HO-1, it may also trigger other signaling pathways that regulate MCP-1 expression independently of HO-1. Indeed, the authors state that there is a delayed phase of MCP-1 in these conditions that is HO-1 independent, which may suggest that hemin co-induces HO-1 with MCP-1 to function as a negative regulator of MCP-1. HO-1 also decreases interferon-beta (IFN- β) [222] and interferon-gamma expression (IFN- γ) [266], which may serve either pro- or anti-inflammatory functions depending on the cell-type and surrounding cytokine milieu. Fig. (2) illustrates some of the signaling interactions described here.

THERAPEUTIC POTENTIAL OF EXOGENOUS INDUCERS OF HEME OXYGENASE-1 EXPRESSION

Since HO-1 initiates potent endogenous antioxidant responses, induction of HO-1 expression has therapeutic potential for several diseases in which oxidative stress is symptomatic, including HIV infection. Treatment of mice with cobalt IX protoporphyrin (CoPP), a powerful HO-1 inducer, was shown to promote graft survival in a model of kidney transplantation [266]. However, HO-1 inducers used *in vitro*, including LPS, hemin, or proto- or mesoporphyrins, have limited clinical relevance given the range of negative side effects and/or limited tolerability or bioavailability. Gene-therapy models have also been developed to more permanently induce HO-1 in target cell types [260, 279]. While promising, this type of approach may be beneficial only in certain conditions, and such therapies have not yet been fully validated in the clinical setting. A more immediate and simpler approach is the use of orally available compounds that can induce HO-1 *in vivo*.

Many studies have shown that a number of plant-based extracts (phytopharmaceuticals) induce HO-1, leading to ameliorated oxidative stress and inflammation. The sources of these compounds are several different plant species and plant organs, ranging from seeds to fruits to leaves to roots [238, 245, 247, 280-293]. Some of these compounds can be

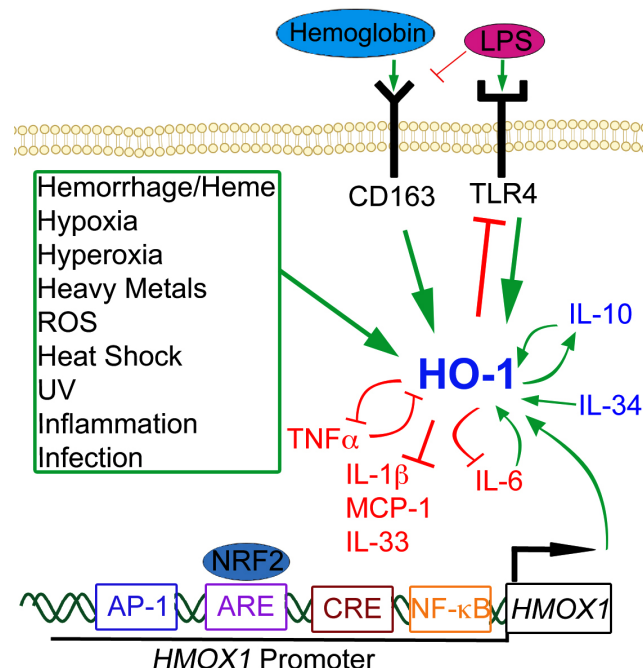


Fig. (2). Signaling Pathways of HO-1. Green arrows represent increased HO-1 expression or activity. Red blocked lines represent inhibition or decreased expression. Several noxious stimuli, highlighted in the green box, are known inducers of HO-1, as well as hemoglobin/heme through the CD163 receptor and LPS through the TLR4 receptor. Anti-inflammatory cytokines are represented in blue; pro-inflammatory cytokines are depicted in red. There are many cytokine signaling loops that involve HO-1 activity or expression, including a positive feedback loop between HO-1 and IL-10 (anti-inflammatory), and a negative feedback loop between HO-1 and TNF- α (pro-inflammatory). Several transcription factors can also bind to the HO-1 promoter (*HMOX1* is the gene symbol for HO-1), notably NRF2 at the ARE site, but also AP-1, CREB, and NF- κ B can bind to the promoter at independent binding sites and induce HO-1 expression.

found in commonly-used plants, such as brown rice [294], Chinese cinnamon [295] or Ginkgo biloba [243, 296]. Curcumin and omega-3 fatty acids are well-studied natural compounds with antioxidant and anti-inflammatory properties that might be related to their potent induction of HO-1 [270, 297-300], although it is not clear if their effects are directly due to their induction of HO-1. As dietary compounds that can be administered orally, such phytopharmaceuticals offer the promise of easily available therapy with potentially high tolerability. However, caution must be prioritized in directly translating these *in vitro* studies to the clinical setting, as no rigorous clinical trials have been performed for many of these compounds. The question of dosage, metabolism and bioavailability will need further and extensive study to determine the efficacy and safety of such compounds as a form of treatment.

Currently, there are two classes of FDA-approved drugs that have the immediate potential for testing HO-1 induction in clinical trials: statins and fumaric acid esters (FAEs). Statins have been widely prescribed to reduce cholesterol

levels by inhibiting HMG-CoA reductase [301]. However, *in vitro* and *in vivo* rodent models have shown that statins can robustly induce HO-1 in monocytes/macrophages, leading to reduction of inflammation [302-305]. BBB-permeable statins therefore have the potential to induce HO-1 in cells of the CNS, including macrophages, microglia, and astrocytes, although such studies have yet to be reported.

Fumaric acid esters, on the other hand, have a demonstrated effect in the CNS. In particular, a formulation of dimethyl fumarate (DMF) trade-marked as Tecfidera, was approved by the FDA on March 27, 2013 for the treatment of multiple sclerosis (MS). DMF is orally delivered, and is quickly metabolized to monomethyl fumarate (MMF), and both compounds exert similar, though not equivalent, biological activities (for review see Gill & Kolson 2013 [306]). DMF functions as an immune modulator, and it was initially approved to treat psoriasis in Germany [307, 308]. Work from our lab has demonstrated that DMF/MMF can robustly induce HO-1 in macrophages [158], and others have shown the same effect in type II dendritic cells [309]. Furthermore, we have shown that DMF/MMF treatment of HIV-infected macrophages significantly attenuates the release of soluble neurotoxins. Pre-treatment of macrophages with DMF/MMF before HIV inoculation reduces HIV infection [158]. The reduction of neurotoxin release is clearly mediated by the increased HO-1 elicited by DMF/MMF, while the suppression of HIV infection might be related to inhibition of NF- κ B translocation [158]. The inhibition of HIV replication by HO-1 induction has also been previously observed in monocytes, using hemin as a stimulant [310], and in MDM using LPS to induce HO-1 [311]. The correlation with increased HO-1 and decreased HIV replication has been recently demonstrated in clinical studies in which HIV+ patients with lower HO-1 expression were found to have higher levels of viremia (when removed from cART) [312]. The effects of HO-1 induction in the CNS of HIV+ patients and its relation to HAND remain to be examined; however, given the proven CNS efficacy of DMF in suppressing inflammation and immune activity in MS patients, DMF stands as a compelling candidate for HAND and other HIV-associated disorders in other tissues (kidney, liver, heart, bone) not derived from opportunistic infections.

CONCLUSION

As this review highlights, there are several pathways through which HO-1 may be induced or activated, in monocytes/macrophages (the primary HIV reservoir in the CNS) and in CNS cells such as astrocytes and microglia, and even neurons in certain circumstances. Increased HO-1 expression in these cell types has the potential to reduce several salient features of HAND and other HIV associated end-organ diseases that have oxidative stress and chronic immune activation as common symptoms. Several classes of pharmaceuticals, from fumaric acid esters (e.g. DMF or MMF) to statins to phytochemicals, have the potential to target these pathways to be tested or developed for HIV adjunctive therapy in addition to current anti-retroviral therapy, and may also aid in the treatment for other neurodegenerative diseases such as Alzheimer's or Parkinson's disease.

LIST OF ABBREVIATIONS

AP-1	=	Activator protein 1
ARE	=	Antioxidant response element
BBB	=	Blood-brain barrier
cART	=	Combined anti-retroviral therapy
CNS	=	Central nervous system
DC	=	Dendritic cell
DMF	=	Dimethyl fumarate
HAND	=	HIV-Associated Neurocognitive Disorders
HIV	=	Human immunodeficiency virus
HIVE	=	HIV Encephalitis
HIV-MDM	=	HIV infected monocyte-derived macrophage
HO-1	=	Heme oxygenase-1
HSV-1	=	Herpes simplex virus-1
IFN β	=	Interferon-beta
IFN γ	=	Interferon-gamma
IL-10	=	Interleukin 10
IL-1 β	=	Interleukin 1 beta
LPS	=	Lipopolysaccharide
MCP	=	Monocyte chemoattractant protein 1
MDM	=	Monocyte-derived macrophage
MMF	=	Monomethyl fumarate
MS	=	Multiple sclerosis
NF- κ B	=	Nuclear factor kappa B
Nrf2	=	Nuclear factor erythrocyte-2 related factor 2
PBMC	=	Peripheral blood mononuclear cells
PNS	=	Peripheral nervous system
ROS	=	Reactive oxygen species
TBI	=	Traumatic brain injury
TLR	=	Toll-like receptor
TNF α	=	Tumor necrosis factor alpha

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

Declared none.

HUMAN/ANIMAL RIGHTS

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