



OPIOID ANALGESICS AND HIV ASSOCIATED NEUROPATHIC PAIN

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ABSTRACT

Opioids are frequently used as analgesics by HIV patients. Contrary to popular belief, new clinical data show that using opioid analgesics frequently really worsens the state of chronic pain. The World Health Organization's most recent study estimates that there are roughly 37.9 million HIV/AIDS patients worldwide. Around 30- 40% of them experience HIV-related discomfort. A significant percentage of chronic pain is neuropathic pain, which is described as chronic pain brought on by diseases or lesions of the nerve system and manifesting as a variety of symptoms of the neurological system, including both positive and negative signals. HIV-related neuropathic pain is believed to be generated by a maladaptive process that initially served to promote regeneration and healing injury induced by HIV protein, central and peripheral sensitization, and side effects of antiretroviral medication. It has been discovered that Gp120, an HIV envelope protein, is the main toxin that causes neuropathic pain. In particular, during HIV infection, the microglia, which release a variety of pro-inflammatory molecules (including TNF, IL-1, and IL-6), not only cause the neurons to become more sensitive, but they also play a key role in the cross-talk connecting the astrocytes and oligodendrocytes to create the central sensitization. This review mainly focus on the mechanism of hiv related neuropathic pain and association with opioids

INTRODUCTION

Combination antiretroviral therapy (cART) has brought about a new era in the treatment of HIV, particularly by giving rise to a new patient population known as persons living with HIV (PLWH). However, PLWH mortality and treatment compliance are affected by a number of consequences in addition to the immunodeficiency disease brought on by HIV infection.¹ According to the International Association for the Study of Pain (IASP), chronic pain is defined as pain that lasts or recurs for longer than 3months, which is one of the consistently encountered symptoms in PLWH and is significantly associated with disability in daily activities, unemployment, and reduced quality of life². Numerous types of chronic pain, such as spontaneous pain (continuous or episodic), hyperalgesia (exaggerated reactions to typically unpleasant stimuli), and mechanical allodynia are frequently classified as neuropathic pain (a painful response to a normally nonpainful stimulus)³. More than 55% of HIV/AIDS patients

report that chronic pain has a negative impact on their quality of life.⁴ For these patients, current therapeutic management frequently relies on long-term usage of prescribed opioid analgesics.⁵ Unfortunately, new clinical data show that frequent use of opioid analgesics in HIV patients causes peripheral neuropathy and chronic pain in addition to the potentially acute analgesic effect.⁶ The possibility that HIV patients taking opioids for pain relief may paradoxically suffer increased pain as a result of treatment raises the clinical significance of this adverse effect.

A maladaptive response to tissue injury in the nervous system, neuroinflammation recruits immune cells and releases mediators to aid in healing and regeneration. When HIV-related glycoproteins (like gp120) are combined and released, it damages neurons and causes neuroinflammation through a number of subsequent changes. This increases the interactions between neurons and glial cells and leads to central sensitization and/or peripheral sensitization. In patients or rodent models, these reactions appear as chronic neuropathic pain. The HIV medications nucleoside analogue reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) also have neurotoxic side effects that exacerbate PLWH's neuropathic pain complaints.⁷

Recent clinical evidence indicates that long-term opioid analgesic usage paradoxically increases pain sensitivity, a condition known as opioid-induced hyperalgesia (OIH).⁸ The typical practise of dose escalation, which can eventually result in the issues associated with overdose, may be facilitated by OIH expression.⁹ Neuroinflammation, demonstrated by glial response and elevation of proinflammatory cytokines rooted in HIV-1-associated pain, is another hypothesised pathogenic mechanism of OIH. As a result, through similar signalling pathways, there may be a pathogenic connection between OIH- and HIV-1-associated discomfort. For instance, morphine tolerance, dependency, and reward are likewise regulated by the HIV-1 gp120 coreceptors CCR5 or CXCR4.¹⁰

THE MECHANISM BEHIND NEUROPATHIC PAIN CAUSED BY HIV

Peripheral sensory neuropathy, which is a type of the so-called "dying-back" degeneration of sensory neurons, is frequently linked to pathological pain in HIV patients¹¹. While the causes of non-neuropathic chronic pain in various areas (such as the musculoskeletal system) remain unknown, it has been demonstrated that HIV-related neuropathic pain is brought on by the neurotoxic effects of the virus and the medications used to treat HIV¹². Although productive HIV infection does not exist in neurons, viral proteins do interact with neurons, glial cells, and immune cells in the central and peripheral nervous systems to cause the development of neuroinflammation, macroscopic hyperalgesia, and allodynia. This process may be made worse by antiretroviral medications.

VIRAL PROTEIN GP120 IS THE MAJOR TOXIN INDUCING THE NEUROPATHIC PAIN

When the CD4 receptor and the C-C chemokine receptor 5 (CCR5)/CXC chemokine receptor 4 (CXCR4) co-receptor are engaged, the HIV envelope glycoproteins gp120 and gp41 go through receptor-driven conformational changes that allow the union of the viral and host cell membranes. Gp120 causes hyperalgesia by directly activating the CXCR4 and/or CCR5 chemokine receptors in dorsal root ganglion (DRG) neurons because infection seldom affects neuronal cells.¹³ Other HIV proteins including Tat (transactivator of transcription) and Vpr (viral protein R) have also been shown to be associated with neuropathic pain, but more compelling evidence points to gp120 as a main cause. Gp120 levels in the dorsal horn of the spinal cord are roughly ten times higher in HIV patients with pain than in those without pain. Tat and Vpr, in contrast to gp120, did not significantly differ between pain-positive and pain-negative HIV patients in the dorsal horn of the spinal cord. There is proof that gp120 directly contributes to the development of allodynia.¹⁴

By activating voltage-gated potassium (Kv) channels in neurons, gp120 and CXCR4 enhance the amount of K⁺ that exits the cytomembrane. Caspase-3 activation follows transitory outward K⁺ currents and results in neuronal damage (Chen et al., 2011). Gp120 causes intracellular calcium changes via a CXCR4-dependent pathway, resulting in neuronal injury.¹⁵

CENTRAL SENSITIZATION AND PERIPHERAL SENSITIZATION IN HIV-RELATED NEUROPATHIC PAIN

Neuropathic pain is caused by damage to the nerves, such as infection, inflammation, or drug toxicity. It affects both the central and peripheral nervous systems, increasing the responsiveness of nociceptive neurons to normal or subthreshold afferent input and decreasing the threshold of nociceptors to stimulation of their receptive fields, which leads to the growth and progression of disease. The progression of neuropathic pain is significantly influenced by the activation of non-neuronal cells, including immune cells and glial cells in both the CNS (such as microglia and astrocytes) and PNS (such as macrophages, Schwann cells, and satellite cells), which are triggered by the release of cytokines, chemokines, and neurotransmitters.¹⁶ High amounts of CD4 and CCR5 are expressed by macrophages and microglia, making them a prime target for HIV infection and providing a reservoir for virus reactivation and replication. It is noteworthy that intact HIV can infect both microglia and astrocytes while crossing the blood-brain barrier (BBB) via transcytosis or paracellularly. The viral protein gp120 may play a crucial role in deciding whether free virus can cross the BBB. Damage to peripheral or central pain transmission neurons may result from noxious substances released from immune-activated, HIV-infected, or gp120-stimulated macrophages and microglia, either directly or indirectly through a cascade in pro-inflammatory pathways, both of which cause hypersensitivity and allodynia related to neuropathic pain.¹⁷

ANTIRETROVIRAL DRUGS LEAD TO NEUROPATHIC PAIN

The creation and expansion of HAART has significantly decreased HIV-related morbidity and mortality, relegating HIV to the status of a chronic inflammatory disease. Despite lower HIV loads, long-term cART therapy is linked to the emergence of neurological diseases.¹⁸ Neuropathic pain is a prevalent neurological disease brought on by cART side effects. Didanosine (ddI), zalcitabine (ddC), stavudine (d4T), and zidovudine (AZT) are among NRTIs that are neurotoxic and essential for causing neuropathic pain.¹⁹

Among these NRTI medications, D4T and ddC are well-known, and both in vitro and in vivo studies have been done on their toxicity. In low-income nations with insufficient resources, D4T is frequently utilised as the first-line regimen²⁰. The risk of peripheral neuropathy, hyperlactatemia, and other illnesses is raised with D4T-based ART. D4T or ddC intraperitoneally injected to treat mechanical and cold allodynia in rats. Transcriptome sequencing performed on mice that had received injections of ddC revealed that the expression of 135 genes had undergone significant alterations. These changes were primarily enriched in the regulation of transcription, multicellular organism development, and cell differentiation. The pro-nociceptive chemokines MCP-1, stromal cell-derived factor-1 (SDF-1), and TNF are increased in DRG after exposure to ddC²¹. Treatment with AZT/Lamivudine/d4T in mice increased TNF, IL-1, and IL-6 in several CNS regions via a Wnt5a-dependent mechanism. Direct evidence was reported by that ddC up-regulates TNF and IL-1 and promotes neuroinflammation in the spinal cord. Activating astrocytes and microglia in a mouse model results in allodynia, which is managed by spinal Wnt5a.²²

PIs are another cause of neuropathic pain. Indinavir, saquinavir, and ritonavir are associated with neuropathic pain in HIV-positive patients, and indinavir has a particular cytotoxic effect on macrophages in the DRG that results in neuronal shrinkage and neurite retraction. Adult rats using indinavir develop mechanical hypersensitivity in their hind paws independent of HIV infection. The PI treatment activates microglia in the lumbar spinal dorsal horn by triggering the phosphorylation of p38, simulating the clinical features of PI-treated HIV patients.²³

REPEATED MORPHINE TREATMENT EXACERBATES GP120-INDUCED HYPERALGESIA

To research how long-term opiate medication affects pain from HIV. Male mice were given intrathecal injections of gp120 (100ng) every other day (days 0, 2, 4, and 6), while gp120 animals were given intraperitoneal injections of morphine (20 mg/kg) every day for a week. The results showed that mice experienced hyperalgesia after just one gp120 injection, which peaked at day three after the second gp120 injection, and continued for at least seven days, in contrast to control animals injected with heat-inactivated gp120 protein. Following day 3, repeated doses of morphine also led to hyperalgesia, though to a lesser amount than gp120 had. This suggests the establishment of opioid-induced hyperalgesia. The addition of morphine increased the gp120-induced hyperalgesia when compared to gp120 therapy alone. This became clear after day 4, when the mechanical withdrawal threshold of the combined treatment

group was 0.560.06g (gp120 alone) or 0.990.11g (morphine alone), demonstrating that morphine treatment enhanced the hyperalgesia generated by gp120.²⁴

Reactive glia may have a role in the emergence of HIV-related pain in human patients as well as in animal models of gp120- or opioid-induced hyperalgesia. So, we were interested in testing the idea that morphine increased SDH glial activation, which in turn increased HIV-associated pain. According to observations, treatment with gp120 or morphine boosted GFAP expression by 60% and 50%, respectively. Pro-inflammatory cytokines were produced by activated astrocytes, and mature IL-1 expression was enhanced. Comparable profiles of TNF- rise were seen after treatment with gp120 and/or morphine.²⁵

In addition to being connected to neuropathic pain brought on by HIV, ROS are also linked to opioid-induced analgesic tolerance and hyperalgesia. Recently it has been noted that both morphine and HIV proteins dysregulate ROS production in mitochondria. Although reactive astrocytes are the primary cell type that collect ROS in the SDH in response to the co-administration of gp120 and morphine, we cannot rule out the possibility that other brain cells may also experience ROS-induced oxidative stress. Indeed, it has been observed that the injection of gp120 and opioids causes both neurons and microglia to create ROS. Morphine's ability to potentiate HIV-related pain is greatly influenced by ROS, particularly in reactive astrocytes. This finding suggests that ROS are a viable therapeutic target for reducing an opioid analgesic's adverse effects on HIV-related pain.²⁶

CONCLUSION

In the current opioid epidemic crisis, HIV patients who abuse opioids have significantly increased Opioid abusing HIV patients are more susceptible to developing more severe symptoms of neuroAIDS, including sensory neuropathy, gliosis, neuro-inflammation, behavioral and cognitive perturbations, and dementia. One third of the people living with HIV suffer painful peripheral neuropathies. The HIV 1 coat protein gp120 is the one linked to genesis of neuropathic pain. Repeated administration of morphine led to increased levels of the pro-inflammatory cytokines IL-1 and TNF-, as well as astrocyte activation in the spinal dorsal horn (SDH). Moreover, we found that the SDH of the HIV pain model, particularly on astrocytes, included mitochondrial reactive oxygen species (ROS) that were potentiated by morphine treatment. Our results indicate that ROS play a significant role in mediating the way that morphine exacerbates gp120-induced pain.

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