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Narrative Review

Treatment Considerations in Painful HIV-Related Neuropathy

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Background: Human immunodeficiency virus (HIV)-related distal sensory polyneuropathy (DSP) is the most common HIV-associated sensory neuropathy. The envelope glycoprotein of HIV-1, gp 120, appears to contribute to this painful neuropathy. Two standard treatments for HIV infection/HIV-related painful DSP (e.g., antiviral therapy [e.g., nucleoside reverse transcriptase inhibitors (NRTI)] opioids) should each be carefully evaluated prior to being utilized to ameliorate the pain of DSP, since they may actually promote nociception.

Nucleoside reverse transcriptase inhibitors require activation in the cell via the addition of 3 phosphate groups (by cellular kinases) to their deoxyribose moiety, to form NRTI triphosphates. Subsequently, these deoxynucleotide analogs compete with natural deoxynucleotides for incorporation into the growing viral DNA chain. The incorporation of NRTIs into the viral DNA chain leads to chain termination; since the nucleoside reverse transcriptase inhibitors lack a 3′-hydroxyl group on the deoxyribose moiety (unlike natural deoxynucleotides), so that the next incoming deoxynucleotide cannot form the next 5′-3′ phosphodiester bond needed to extend the DNA chain.

Unfortunately, many conventional agents utilized as pharmacologic therapy for neuropathic pain are not effective for providing satisfactory analgesia in painful HIV-related distal sensory polyneuropathy. Although there is no robust data, there does seem to be information which would support the notion of opioids having increased risk of being particularly pronociceptive when being used to treat painful HIV-related neuropathy. It thus appears conceivable that the use of at least certain opioids in efforts to achieve analgesia in patients with painful HIV-related neuropathy may be less than ideal since at least certain opioid analgesics themselves may potentially contribute to "fueling the fire" of HIV enhanced pain hypersensitivity; at least in part via upregulation of specific chemokine receptors (e.g., CXCR4) which seem to be vitally important in promoting HIV-related pain facilitation. The risk benefit ratio of treatment with agents such as NRTIs as well as opioids should be reviewed for specific individual patients, prior to clinicians initiating these agents.

Objectives: To raise awareness of the theoretical potential downside that opioids may possess if they are used for the treatment of painful HIV-related neuropathy.

Methods: A narrative review of selected literature.

Limitations: Hypothetical in nature.

Conclusions: Clinicians should consider all aspects of various therapeutic options, carefully weighing the risk/benefit ratios of each potential treatment before initiating opioids for painful HIV-related neuropathy.

Key words: Human immunodeficiency virus, acquired immune deficiency syndrome, distal sensory polyneuropathy, pain, glia, neuropathy, opioids, nucleoside reverse transcriptase inhibitors

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The global human immunodeficiency virus (HIV) prevalence is estimated at 33 million persons(1). Those infected with HIV-1 experience many unrelieved symptoms. Aouizerat and colleagues (2) found that pain was highly prevalent (55%) in people living with HIV disease, and was associated with immune status (CD4+ T-cell count), race, and sleep disturbance, but not with age, gender, or symptoms of fatigue, depression, or anxiety. HIV-1 infection is associated with multiple sensory and motor neuropathies (3-5), in spite of the fact that HIV-1 does not replicate especially well in neurons. It has been suggested that the interaction of viral proteins, glia, and cytokines/chemokines may partially mediate viral effects on neuronal function (6).

1.0 HIV-Related Painful Distal Sensory Polyneuropathy

HIV-associated sensory neuropathy is the most common neurological complication of HIV infection, and may affect one-third of AIDS patients (7, 8). HIV-related painful distal sensory polyneuropathy (DSP) is the most common HIV-associated sensory neuropathy, generally involving the extremities. Clinical examination plus electrophysiology found that DSP affects 36% of HIV-infected patients being treated with highly active antiretroviral therapy (HAART), although it may remain subclinical in about two-thirds of cases. Important risk factors include: age, severe prior immunosuppression and treatment with the combined use of zalcitabine (ddC), stavudine (d4T) and didanosine (ddI) (9). HIV-related painful DSP appears to affect one-third or more of all patients infected with HIV-1; up to about 40% of HIV-infected individuals treated with antiretroviral therapy (ART) may experience significant pain (1,9). The clinical picture may resemble diabetic or alcoholic distal symmetric polyneuropathy. Initial discomfort generally begins with parasthesias in the fingers and toes followed by burning or lancinating pain, weeks to months later. HIV-related painful DSP is a clinical diagnosis but in those with advanced HIV-1 infection, epidermal nerve fiber density (ENFD) assessment correlates with the clinical and electrophysiologic severity of DSP (10).

Robinson-Papp et al (11) analyzed data that were obtained from the Central Nervous System HIV Antiretroviral Therapy Effects Research (CHARTER) study. The results of Robinson-Papp et al (11) suggest that HIV-infected patients reporting symptoms consistent with HIV-associated sensory neuropathy (HIV-SN), such as tingling, pins and needles, or aching or stabbing pain in the distal lower extremities, usually have objective evidence of HIV-SN on neurologic examination or with neurophysiologic testing. This finding holds true regardless of demographic factors, depression or substance use history. Furthermore, increasing intensity of pain measured on a visual analog scale was associated with increasing severity of sensory abnormality (11).

Although the precise mechanisms which account for the pain of HIV-related DSP remain uncertain, they are probably not largely due to direct effects of active infection of peripheral neurons by the virus. Multiple factors likely contribute to HIV-related painful DSP, however it appears that indirect effects of the HIV-1 virus itself are at least partially involved.

2.0 Potential Pathophysiology Of Hiv-Related Painful Dsp

Although the precise mechanisms involved in HIV-related painful distal sensory polyneuropathy (DSP) remain uncertain; preclinical studies suggest that gp 120, an envelope glycoprotein of HIV-1, may play a central role (12). Spinal cord glia (microglia and astrocytes) have been shown to play a key role in contributing to the facilitation of certain pain states (13-15). It has been proposed that gp 120 interacting with chemokine receptors CXCR4 and CXCR5 (located on neurons, astrocytes and microglia) may contribute to HIV-related painful DSP (16). Perineural HIV-1 gp 120 treatment induced a persistent mechanical hypersensitivity (44% decrease from baseline) but no alterations in sensitivity to thermal or cold stimuli, and thigmotactic (anxiety-like) behavior (16). The mechanical hypersensitivity was responsive to systemic treatment with gabapentin, morphine, and the cannabinoid WIN 55, 212-2, but not with amitriptyline (16).

Elevation of intracellular calcium is required for facilitation of neuronal nitric oxide synthase (nNOS) (17), which leads to increased nitric oxide (NO). Holguin et al (18) suggested that NO is necessary (but perhaps not sufficient) for at least some gp 120-induced responses. NO may act largely by amplifying parallel actions of gp 120 on glial transcription factors and/or glial proinflammatory cytokine release (18). Holguin et al (18), studying an animal model of mechanical allodynia induced by intrathecal gp 120, found that pretreatment using L-NAME, a broad-spectrum nitric oxide synthase (NOS) inhibitory or 7-NINA, a selective inhibitor of NOS type-1 (nNOS), equally abolished the behavioral effects of gp 120-induced mechanical allodynia.

Minami et al (19) suggested that one mechanism contributing to gp 120-induced increases in intracellular calcium may be a gp 120-mediated increase in cyclooxygenase action with resultant increased PGE$_2$. Minami further postulated that PGE$_2$ binding to the EP3 receptor may lead to the release of an endogenous kappa-opioid ligand (e.g., dynorphin) which binds to the kappa opioid receptor (KOR) --- mediating a rapid prominent rise in [Ca^{2+}] in a group of dorsal horn cells in the spinal cord (19).

Activated glia release pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF], interleukin-1β [IL-1], and interleukin-6 [IL-6]). Spinal TNF and IL-1 mRNA expression, protein production, and release are increased in response to various pro-nociceptive stimuli (20-22). Intrathecal TNF and intrathecal IL-1 elicit pain behaviors (23) and facilitate neuronal sensitivity to nociceptive stimuli (24). Furthermore, disruption of TNF and IL-1 spinal cord signaling (using TNF soluble receptor and/or IL-1 receptor antagonists [IL-1ra]) have been reported to ameliorate pain facilitation in a wide variety of animal models (12, 20, 22, 25-28).

IL-1 and TNF may act at least partly via p38 mitogen-activated protein kinase (p38MAPK) cascades in glia (29, 30). Milligan et al (21) demonstrated that systemic administration of the p38MAPK inhibitor CNI-1493 (which can cross the intact blood-brain barrier), blocked centrally mediated exaggerated pain states (thermal hyperalgesia and mechanical allodynia) induced by intrathecal gp 120 (most likely via interfering with proinflammatory cytokine signal transduction).

The actions of IL-6 in gp 120-enhanced pain states appear to be pro-nociceptive in nature (31). Schoeniger-Skinner et al (31) suggested that blockade of IL-6 inhibits gp 120-mediated increases in TNF, IL-1, and IL-6 mRNA in the dorsal spinal cord, as well as TNF and IL-1 protein release into the surrounding cerebrospinal fluid. Thus, it would seem that IL-6 may lead to pain facilitation at least in part via stimulating the production and release of other pro-inflammatory cytokines (e.g., TNF, IL-1) (31). Growing evidence supports that proinflammatory cytokines (e.g., TNF, IL-1) released by activated spinal glial cells and within the dorsal root ganglia (DRG), are crucial nociceptive mediators which contribute to enhanced pain in animal models of HIV-related painful DSP (31). It also appears that spinal proinflammatory cytokines may play a nociceptive role in contributing to the pain of AIDS therapy-induced neuropathy. Furthermore, in other models of neuropathic pain (e.g., chemotherapy-induced painful neuropathy), it has been proposed that targeting the production of proinflammatory cytokines via inhibition by intrathecal IL-10 gene therapy may be a promising therapeutic strategy for the relief of paclitaxel-induced neuropathic pain (32).

There are at least 2 ways in which HIV-1-induced DSP may involve the direct effects of HIV-1 gp120 on chemokine receptors in the DRG: viral protein shedding in the peripheral nervous system might enable gp120 to produce painful neuropathy via glial to neuronal signaling in the DRG and/or spinal cord (33,34) or by the direct activation of CCR5/CXCR4-bearing sensory neurons by gp120 (35-38). Keswani et al (34,39) have described a model in which gp120 can act in both these ways. They demonstrated that binding of gp120 to CXCR4 receptors expressed by DRG satellite glial cells upregulates the release of the chemokine RANTES, which can then activate CCR5 receptors expressed by DRG neurons (38, 39). Also, gp120 can directly bind to and activate CXCR4 receptors expressed by DRG neurons (36,38). This initial excitation of DRG neurons by gp120 and/or glial mediators might produce Ca2+-dependent upregulation of CCR2 expression by these neurons.

3.0 Nucleoside Reverse Transcriptase Inhibitors Effects May Promote Hiv-Related Painful DSP

Therapeutic agents for the treatment of HIV disease may promote HIV-related DSP. AIDS patients who are treated by HAART agents can also develop a painful sensory neuropathy. The symptoms of this syndrome are clinically indistinguishable from those of HIV-1 induced DSP, including a burning sensation in the hands and feet and hypersensitivity to pain (9,40,41) and for the purpose of this article are grouped together as HIV-related DSP. The mechanisms contributing to AIDS therapy-induced neuropathy may uniquely differ from other painful peripheral neuropathies. Protein kinase C epsilon (PKC$_E$) appears to contribute to the mechanical hyperalgesia of alcohol-induced neuropathy but does not seem to be involved in AIDS therapy neuropathy (42). Nociceptive mechanisms which appear to contribute to AIDS therapy neuropathy involve disturbed calcium homeostasis, caspase signaling, and mitochondrial electron transport (43-45).

Peripheral administration (at the site of nociceptive testing) of antagonists of intracellular calcium (43), caspase signaling (44), and the mitochondrial electron transport chain (45) reverse ddC-induced mechanical hyperalgesia (although they have no effects on mechanical nociceptive threshold in control animals) (46). The predominant mechanism of action of nucleoside reverse transcriptase inhibitors (NRTI)-induced neurotoxicity is believed to be via effects on mitochondrial function (47,48).

Chemokines (**chemo**attractant cyto**kines**) are a class of small (7-10 kDa) proteins originally identified because of their ability to induce migration and activation of certain leukocyte subsets (49). Schwann cells, the ensheathing cells of peripheral nerve axons, may contribute to HIV DSP by producing the β chemokine, RANTES (regulated upon activation, normal T-cell expressed and secreted), which leads to TNF-α mediated neuronal apoptosis via binding to TNFR1 and neuritic degeneration. Under normal conditions chemokine receptors are expressed by numerous DRG satellite glial cells and Schwann cells as well as a limited number of neurons (50,51).

Chemokines and gp 120 produced excitatory effects on DRG neurons, stimulated the release of substance P, and lead to allodynia after injection into a rat paw (36). Oh and colleagues (36) concluded that these results provide evidence that chemokines and gp 120 may produce pain hypersensitivity by directly exciting primary nociceptive neurons via direct actions on neuronal chemokine receptors. Trushin et al (52) concluded that gp 120 interaction with CXCR4 is required for gp 120 apoptotic effects in primary human T cells. The envelope glycoprotein complex (Env) of HIV-1 can induce apoptosis (programmed cell death) via a wide variety of multiple distinct mechanisms. A soluble Env derivative, gp 120, can kill cells through signals which are transmitted by chemokine receptors (e.g., CXCR4) (53). Soluble gp 120 may trigger cell death via interaction with CD4 and/or CXCR4. Binding of gp 120 to CD4 may activate the CD95/CD95L-dependent apoptotic pathway or trigger a Bax-dependent mitochondrial apoptosis, requiring p56 activity (53). Additionally, interactions between gp 120 and CXCR4 may lead to mitochondrial membrane permeabiliation (MMP) (54) through pertussis toxin-sensitive G proteins ($G_{i\alpha}$), p38 MAPK pathway, and/or Ca^{++}-dependent mechanisms (53). Furthermore, cell surface-bound Env (gp 120/gp 41) on the plasma membrane of HIV-1 infected cells can kill uninfected bystander cells expressing CD4 and CXCR4 (or similar chemokine receptors) by at least 3 mechanisms (53).

First, a transient interaction between Env and CD4/CXCR4/5 involving a "hemifusion-mediated" exchange of membrane lipids may lead to the selective death of single CD4-expressing target cells (53). Second, fusion (initially cytoplasmic and then nuclear fusion) of Env-expressing cells with Env-negative cells may occur and lead to the formation of syncytia, which ultimately results in activation of the mitochondrial pathway of apoptosis after a period of latency. Multiple transcription factors (e.g. p53, NF-kB) kinases may be involved in these complex processes including: cyclin-dependent kinase-1 (CdK1), checkpoint kinase-2 (ChK2), mammalian target of rapamycin (mTOR), p38 mitogen-activated protein kinase (p38MAPK), inhibitor of nuclear factor-kappa B kinase (IKK)] (53). Third, an Env-expressing cell at an early ("pre-apoptotic") stage of apoptosis can fuse with a CD4-expressing target cell and precipitate the death of both cells via a process involving mitochondria known as "contagious" apoptosis (53).

In addition to direct effects of HIV-1 contributing to HIV-related painful DSP, another factor which may facilitate HIV-related DSP may be the administration of a nucleoside reverse transcriptase inhibitor (NRTI) which HIV-infected patients may take to treat their HIV disease. Bhangoo et al (51) have postulated that NRTIs, known to produce painful neuropathies and enhance pain hypersensitivity produced by HIV-1 infection, may lead to pain hypersensitivity through the upregulation of CXCR4 signaling in the DRG largely via increased numbers of CXCR4 receptors (51). Rats treated with 2", 3"-dideoxy cytidine (ddC), an NRTI agent for AIDS therapy, produced marked upregulation of CXCR4 mRNA expression in both neurons and glia along with an increase in SDF-1 (the natural endogenous ligand for CXCR4 referred to as CXCL4) mRNA in glial cells (51). Furthermore, administration of the CXCR4 antagonist AMD3100 temporarily reversed ddC-induced pain hypersensitivity (51).

Gp 120 binding to CXCR4 receptors expressed by glia may stimulate the release of SDF-1 or other potential excitatory mediators (55). It is then conceivable that the combination of NRTI treatment (leading to upregulation of CXCR4 signaling) with proalgesic effects from gp 120 (of HIV-1 infection) could yield synergistic effects with respect to neuropathic pain (51). Robinson et al (56) concluded that both HIV proteins and NRTIs cause axonal damage by inducing mitochondrial injury and rearrangement of microtubules (56).

In studies of non-neuronal cells, CXCR4 and SDF-1 have been shown to be downstream targets of the hypoxic induction transcription factor-1 (HIF-1) (57,58). Bhangoo et al proposed that since key actions of NRTIs (which seem to include their interference with mitochondrial function) appear to be linked to HIF-1 activity, the possibility exists that these cellular elements are linked in the regulation of CXCR4 receptors by NRTIs (51).

Utilizing a rodent model that incorporates the viral coat protein, gp120, and the NRTI, 2'3'-dideoxycytidine (ddC), Bhangoo and colleagues (59) examined the degree to which chemokine receptor signaling via CCR2 and CXCR4 potentially affects the resultant chronic hyper-nociceptive behavior. Following unilateral gp120 sciatic nerve administration, rats developed significant tactile hyper-nociception in the hind paw ipsilateral to the gp120 treatment. Using immunohistochemical studies, we demonstrated that MCP1 and CCR2 were upregulated by primary sensory neurons in lumbar ganglia by post-operative day (POD) 14. The functional nature of these observations was confirmed using calcium imaging in acutely dissociated lumbar DRG derived from gp120 injured rats at POD 14. Tactile hyper-nociception in gp120-treated animals was reversed following treatment with a CCR2 receptor antagonist at POD 14 (59). The hyper-nociceptive behavior associated with gp120 plus an NRTI injury plus drug combination was only effectively reversed using the CXCR4 antagonist, AMD3100. These studies indicate that the functional upregulation of CCR2 and CXCR4 signaling systems following a combination of gp120 and an NRTI are likely to be of significant importance to associated painful distal sensory polyneuropathy (59) (Fig. 1).

Schoeniger-Skinner et al (31) tested whether the IL-6 release in the spinal cord contributes to gp 120-induced mechanical allodynia and/or to gp 120-induced increases in TNF and IL-1 (31). An i.t. anti-rat IL-6 neutralizing antibody was used to block IL-6 actions upon its release by i.t. gp 120. This IL-6 blockade abolished gp 120-induced mechanical allodynia (31). The findings of Schoeniger-Skinner and colleagues (31) indicate that a blockade of IL-6 inhibits the gp 120-induced elevations of TNF, IL-1, and

IL-6 mRNA in the dorsal spinal cord, elevation of IL-1 protein in the lumbar dorsal spinal cord, and TNF and IL-1 protein release into the surrounding lumbosacral cerebrospinal fluid. These results would suggest

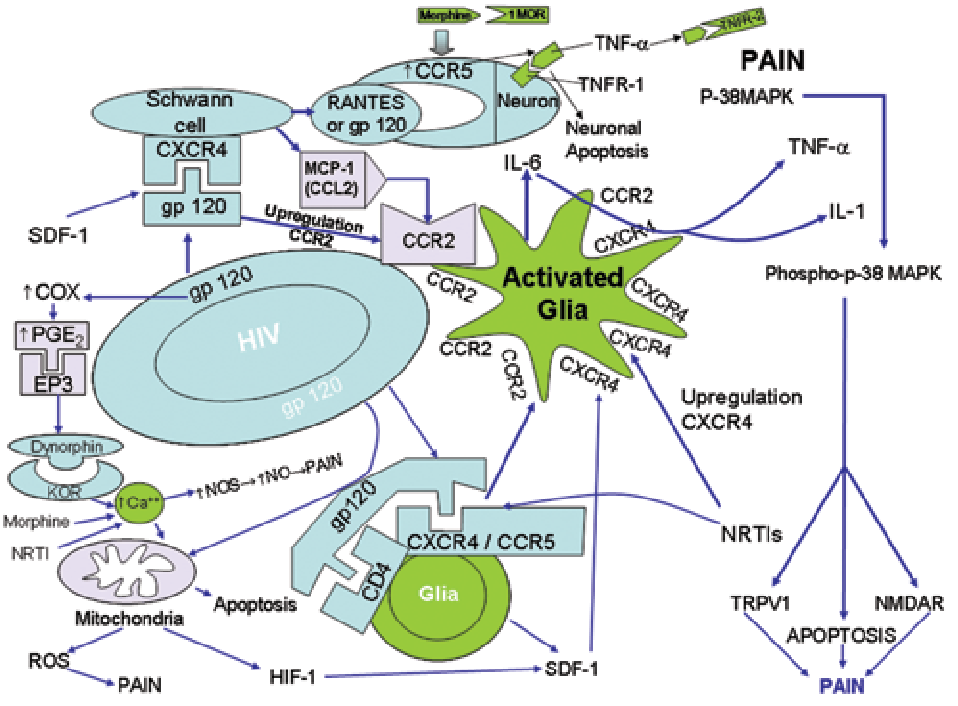

Fig. 1. *Schematic of Potential HIV/NRTI/Opioid Signaling Interactions*

that IL-6 induces pain facilitation, and may do so in part by stimulating the production and release of other pro-inflammatory cytokines (31).

Prosaptide TX14(A) is a peptide derived from prosaposin that alleviates allodynia or hyperalgesia in models of painful diabetic neuropathy, inflammatory pain and neuropathic pain (60-62). Systemic delivery of prosaptide TX14(A) caused a prolonged and dose-dependent protection from onset of gp 120-induced tactile allodynia and also alleviated established tactile allodynia (63). The effective systemic dose of prosaptide TX14(A) was similar to the effective dose against nerve disorders in diabetic rats (60, 64). Intrathecal delivery of 0.5 mg TX14(A) before or after paw gp 120 injection resulted in long lasting prevention and reversal of allodynia, however, intraplantar injection was ineffective (63). The anti-allodynic mechanisms of TX14(A) remain uncertain (63).

Thus, it appears that NRTI administration, in attempts to treat HIV-1 infection, may actually contribute to "fueling the fire" of HIV-enhanced pain hypersensitivity by upregulating specific chemokine receptor functioning which seems to be an integral part of the HIV mechanisms leading to enhanced pain states (e.g., increased numbers of CXCR4 receptors could enhance virion associated gp 120 pain facilitation).

4.0 Treatment of Hiv-Related Painful Dsp

HIV-related DSP appears to be particularly resistant to pharmacologic treatment, and multiple agents that are normally found to be useful in other peripheral neuropathic pain conditions are generally disappointing in the treatment of HIV-related painful DSP. In fact, all "first-line agents," according to 3 separate pharmacologic guidelines and other articles (65-67) to treat peripheral neuropathic pain (68-70) as well as the update 2010 European Federation of Neurological Societies (EFNS) guidelines (71), were not effective for the treatment of HIV-related painful DSP.

4.1 Amitriptyline and Mexiletine

Two trials (72,73) that were included studied the efficacy of amitriptyline. Amitriptyline demonstrated no superiority to placebo in the primary outcome measure. The mean change in Gracely pain scores from baseline to week 14 was 20.26 with amitriptyline (maximum dose 75 mg/d) and 20.30 with placebo (72). The second trial (73) compared amitriptyline, mexiletine, and placebo. This trial was terminated early following an interim review of results. It was deemed by the trial monitoring board that further enrolment into the study was unlikely to detect significant differences in either the amitriptyline or mexiletine arms compared to placebo. No superiority was reported in reducing mean Gracely pain scores (SD) from baseline to the end of treatment week 8 for amitriptyline (maximum dose 100 mg/d) 20.31 (0.31); mexiletine 20.23 (0.41); compared to placebo 20.20 (0.30) (1).

4.2 Gabapentin

Hahn et al (74) compared gabapentin (titrated to a maximum of 2400 mg/d) to placebo in a parallel group multicenter, double-blind, randomized controlled trial (RCT). At the longest treatment period assessed, no difference in efficacy was reported between gabapentin and placebo groups for the primary outcome measure, median change in VAS (is this an abbreviation for visual analog scale?) (0–100 mm) baseline to end of week 4: gabapentin 244.1, placebo 229.8. No indication of variance or P value was documented.

4.3 Pregabalin

One large multi-center RCT (75) examined the efficacy of pregabalin, titrated over 2 weeks to a maximum tolerated dose up to 1200 mg/d, in a multicenter, 14 week parallel group, placebo controlled RCT. No superiority of pregabalin over placebo in the primary pain outcome measure was reported: mean change in NPRS (what is this abbreviation?) baseline to end of week 14: pregabalin 22.88, placebo 22.63, P =0.39.

The lack of efficacy of amitriptyline and pregabalin in HIV neuropathy (72, 73, 75), may in part be explained by the high effects during placebo treatment.

4.4 Lamotrigine

Three trials assessing the efficacy of lamotrigine in painful HIV-SN were identified (1,77-79). One trial (77) enrolled only one painful HIV-SN patient (to the placebo control group) and was therefore excluded from further analysis.

The first study of 42 participants (76) claimed effectiveness for lamotrigine 300 mg/d, but over 50% of the treatment group dropped out making results difficult to interpret. Although in the per protocol (PP) analysis there was some benefit, in the intention to treat (ITT) analysis with "last value carried forward" (LVCF), lamotrigine was not superior to placebo when comparing differences of mean Gracely pain scores (which was the primary endpoint) (76).

The second study (79) analyzed the results according to whether participants were receiving ART or not. For those who were receiving antiretroviral therapy, there did appear to be some benefits in terms of attainment of moderate or better pain relief with lamotrigine (35/62, 57%) than placebo (7/30, 23%). For Patient Global Impression of Change, marked improvement was recorded by 29/62 (47%) of participants on lamotrigine and 4/30 (13%) on placebo with antiretroviral therapy. Thus, Simpson et al (79) did not demonstrate a superiority of lamotrigine over placebo for the primary outcome measure (mean improvement in Gracely pain score) in the total cohort or in either stratum. However, lamotrigine did show superiority to placebo in the neurotoxic ARV-exposed stratum in a secondary outcome measure, mean improvement in VAS baseline to end of treatment, P = 0.003 (79).

Wiffen et al (80) performed a Cochrane Review of lamotrigine for acute and chronic pain and found there is no convincing evidence that lamotrigine is effective in treating acute or chronic pain at doses of about 200-400 mg daily. Almost 10% of participants taking lamotrigine reported a skin rash (80). They concluded that lamotrigine does not have a significant place as analgesic therapy based on available evidence (80).

4.5 Topical Capsaicin

Four trials (78,81-83) were found that assessed topical capsaicin efficacy in painful HIV-related DSP. Of the included trials, one (78) examined the efficacy of topical capsaicin 0.075% cream in a parallel group RCT. The authors stated that no superiority of capsaicin 0.075% over placebo in mean improvement in a numeric rating score (NRS) (0–10) was seen, however only graphical data were presented.

A second study (81) examined topical capsaicin 8%. Participants received either the 8% patch or an active placebo (capsaicin 0.04%) in a single application lasting either 30, 60, or 90 minutes. Following this single application participants were followed-up for 12 weeks. Capsaicin 8% was found to be superior to placebo in the percentage reduction of the NPRS (SD) from baseline to week 2 to 12: 8% capsaicin: 222.8 (30.6); compared to placebo: 210.7 (30.8), (P = 0.0026). Presuming that the control capsaicin 0.04% is a true placebo, an NNT (is this number needed to treat?) of 6.46 95% CI (3.86–19.69) was calculated for treatment with capsaicin 8% patch.

4.6 Topical Lidocaine

Estanislao and colleagues (84) conducted a randomized controlled trial demonstrating that topical lidocaine 5% gel is a safe but ineffective agent in the treatment of pain in HIV-associated DSP (84).

4.7 Smoked Cannabis

A literature search found 4 articles related to cannabinoid use and painful HIV-SN. Only 2 were RCTs (85, 86). The excluded articles included one clinical survey (87) and one review article (88).

Smoked cannabis was reported to be superior to placebo in reducing DDS (what is this abbreviation?) from baseline to end of treatment day 5 in the PP population (86). The median difference between cannabis and placebo was 23.3 out of 20; P = 0.016. No data were reported for the ITT analysis, however the authors stated that the PP analysis was similar to the ITT analysis with p =0.02 (86).

A second study (85) compared smoked cannabis (3.56% D-9- tetrahydrocannabinol t.d.s.) to placebo cigarettes in a parallel group RCT. Smoked cannabis was shown to be superior to placebo in reducing pain from baseline to end of treatment day 5 in the ITT analysis: cannabis 234% (IQR what is this abbreviation?271 to 216), placebo 217% (IQR 229 to 8) p = 0.03. More participants reported > 30% VAS improvement with smoked cannabis compared to placebo: 13/27 and 6/27 respectively (1).

5.0 POTENTIAL FUTURE AGENTS TO TREAT PAINFUL HIV-NEUROPATHY NERVE GROWTH FACTOR (NGF)

One RCT (89) examined the efficacy of subcutaneous recombinant human Nerve Growth Factor (rhNGF) in the treatment of painful HIV-SN. This study assessed 2 doses (0.1 and 0.3 mg/kg) given twice weekly compared with placebo for 18 weeks. rhNGF was superior to placebo for the primary outcome measure in the ITT analysis; median change of the Gracely pain score from baseline to end of week 18: rhNGF 0.1 mg/kg: 20.18 (20.10 to 20.25) P = 0.05, 0.3 mg/kg: 20.21 (20.14 to 20.29) P = 0.04, and placebo: 0.06 (+0.01 to 20.14) (1). (why are you citing ref 1 and not ref 89?)

5.1 Prosaptide and Peptide –T

Two trials (90,91) examined the efficacy of the novel agents in placebo controlled parallel group RCTs. One randomized trial (91) reported the use of subcutaneous prosaptide (maximum dose of 16 mg/d) over 6 treatment weeks and found that although it was safe, prosaptide did not achieve efficacy superior to placebo in the primary outcome measure (mean change in Gracely pain score from baseline to week 6) (91).

5.2 Acetyl –L-carnitine

While acetyl-L-carnitine has been the subject of 6 articles (92-97) in the treatment of painful HIV- related painful DSP, only one was an RCT (96) and eligible for inclusion. This was a parallel group trial of acetyl-L-carnitine (1000 mg/d) and placebo intramuscular injections. In this RCT acetyl-L-carnitine, in an analysis of the PP population, showed a modest superiority to placebo. However an analysis of the ITT population did not show superiority to placebo: mean change in VAS (0–10cm) (SD) from baseline to the end of week 2: acetyl-L-carnitine 21.32 (1.84); placebo 20.61 (1.55) P = 0.07.

Phillips and colleagues performed a systematic review and meta-analysis selecting prospective, double-blinded, randomized controlled trials (RCTs) investigating the pharmacological treatment of painful HIV-SN with sufficient quality assessed using a modified Jadad scoring method (1).

Of 44 studies identified, 19 were RCTs. Of these, 14 fulfilled the inclusion criteria. Interventions demonstrating greater efficacy than placebo were smoked cannabis NNT 3.38 95% CI(1.38 to 4.10), topical capsaicin 8%, and recombinant human nerve growth factor (rhNGF). No superiority over placebo was reported in RCTs that examined amitriptyline (100 mg/d), gabapentin (2.4 g/d), pregabalin (1200 mg/d), prosaptide (16 mg/d), peptide-T (6 mg/d), acetyl-L-carnitine (1 g/d), mexilitine (600 mg/d), lamotrigine (600 mg/d) and topical capsaicin (0.075% q.d.s.what is this abbreviation? Abbreviations such as qd, qid, and qod are not allowed in medical publishing) (1)

Evidence of efficacy exists only for capsaicin 8%, smoked cannabis and rhNGF. However, rhNGF is clinically unavailable and smoked cannabis cannot be recommended as routine therapy. Evaluation of novel management strategies for painful HIV-SN is urgently needed (1).

6.0 Opioids for the Treatment of HIV-Related Neuropathy

At the end of 2007, Dworkin et al (68) updated their last published recommendations of the Neuropathic Pain Special Interest Group from 2003 (98). In the 2003 recommendations, opioids and tramadol were listed as first-line medications for the treatment of neuropathic pain, however, in the 2007 recommendations they have been "cut from the starting team," and relegated to second-line therapy (except in "select clinical circumstances"). Four such circumstances which the authors listed include:

- During titration of a first-line medication to an efficacious dosage for prompt pain relief
- Episodic exacerbations of severe pain
- Acute neuropathic pain
- Neuropathic cancer pain (68).

Dworkin and colleagues (98) add that such "first-line" use of opioids should be reserved for circumstances in which "suitable alternatives cannot be identified and should be on a short-term basis to the extent possible" (98).

Some of the reasons given by Dworkin and colleagues (98) for "axing opioids from the starting line-up of analgesics for neuropathic pain" include:

1. More frequent adverse effects than some first-line agents (99-101) (some of which may persist throughout long-term treatment)
2. The long-term safety of opioid therapy has not been systematically studied (102, 103), and preliminary evidence that long-term opioid therapy may be associated with immunologic changes and hypogonadism (104-106)
3. Experimental data which suggest that opioid treatment may be associated with opioid-induced hyperalgesia (107-110)
4. The potential for opioid analgesic misuse or addiction (68).

Others have also considered opioids as second-line agents (69), or third-line agents (70) for the treatment of neuropathic pain.

In the 2010 revision, the second (EFNS Task Force revised its 2006 guidelines (69) on the pharmacological treatment of neuropathic pain (71). Medications recommended as first line agents for neuropathic pain conditions such as diabetic neuropathy include: tricyclic antidepressants, serotonin and norpinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine), and calcium channel alpha 2 delta ligands (gabapentin, pregabalin) (71). Tramadol and opioids are reserved as second or third line agents (71).

Clinicians prescribing opioids for patients with HIV disease should be cognizant of potential interactions between certain opioids and certain medications used to treat HIV disease. Ritonavir and lopinavir/ritonavir greatly increase the plasma concentrations of oral oxycodone in healthy volunteers and enhance its effect.

When oxycodone is used clinically in patients during ritonavir and lopinavir/ritonavir treatment, reductions in the oxycodone dose may be needed to avoid opioid-related adverse effects (111).

6.1 Opioids May Enhance HIV Disease Progression

It appears that morphine signaling in an HIV-1-infected central nervous system (CNS) resident cell alters the transcriptional profile of the cell and enhances neurotoxicity. Activation of protein kinase A (PKA) leads to phosphorylation of the transcription factor cAMP response element binding (CREB) protein, and the now active CREB binds cAMP response element (CRE) sequences within the promoter region of the target genes (112). These target genes include the HIV-1 LTR, leading to increased viral transcription, as well as the HIV-1 coreceptors CXCR4 and CCR5, leading to increased expression of the receptors on the cell surface, potentially enhancing infection by HIV-1 (112). Cytoplasmic Ca2+ levels also increase. Increased viral synthesis; increased production and secretion of the viral proteins gp120 and Tat, along with host proteins RANTES, MCP-1,5, IL-1β, IL-6, and TNF-α, and increased levels of glutamate and aspartate in the CSF affect surrounding neurons (112). High levels of Tat, gp120, IL-1β, IL-6, and TNF-α lead to the phosphorylation and activation of p38/MAPK, triggering a signaling cascade and the increased presence of aspartate and glutamate may also lead to excitotoxicity (112).

Few in vitro studies have been published to date that directly test the effect of morphine on HIV-1-infected cells of the CNS. Bokjari et al (113) demonstrated in murine microglial cells that morphine treatment could enhance CCR5 expression as well as induce an activated cell phenotype. Reynolds and colleagues (114) revealed that heroin was shown to potentiate HIV-1 replication in normal human astrocytes.

Infection with a triple combination of SIV/17E-Fr, SHIV89.6P, and SHIVKU strains led to rapid disease progression with high plasma viremia, a large decline in the numbers of circulating CD4+ T cells, and rapid ablation of the adaptive immune response in 50% of morphine-dependent macaques as well as high cerebrospinal fluid (CSF) viral loads and marked neuropathogenesis, culminating in mortality by 20 weeks postinfection not observed in the nonaddicted, infected macaques (115, 116). In efforts to investigate the in vivo effects of morphine on HIV infected primates in a nonhuman primate model, Bokhari and colleagues (117) utilized Indian rhesus macaques infected with SIVmacR71/17E and demonstrated the macaques, which received morphine and virus (M+V), exhibited a trend towards higher mortality rates, retardation in weight gain, and higher plasma and CSF viral loads. A subset of M+V animals succumbed to disease within weeks postinfection, had a higher incidence of other end organ pathologies and therefore were classified as rapid progressors. The M+V animals, but especially the rapid progressors, also exhibited a trend toward increased virus build-up in the brains along with an increased influx of CD68+ infected monocyte/macrophages in the brain (117).

Evidence linking opioid abuse to HIV-1 neuropathogenesis in humans includes autopsy samples from the Edinburgh HIV-1/AIDS cohort, which have shown that in AIDS patients, HIV-1 encephalitis was more likely to be found in opiate abusers than in those homosexual men who did not abuse drugs(118).

The HIV-1 long terminal repeat (LTR), which serves as the viral promoter, contains a CRE sequence upstream of the transcription start site. Morphine may directly induce HIV-1 transcription through upregulation of ATF/CREB factors that bind the CRE element, resulting in increased viral replication. Banerjee and Wigdahl (112) recently demonstrated that the phosphoactivating transcription factor/CREB protein binds to this site in response to specific cAMP activators like forskolin. Furthermore, MOR (what is this abbreviation?) signaling may indirectly modulate the expression of the chemokine co-receptor CCRS via effects on the cAMP/PKA/CREB pathway (119).

μ-opioids can directly enhance neurotoxicity either by acting on the neuron directly or by enhancing HIV-1 replication in infected cells of the CNS, thereby inducing secretion of known HIV-1 neurotoxic proteins (Tat, Nef, gp120, and Vpr) or induction of other potentially toxic products such as proinflammatory cytokines, glutamate, arachidonic acid, reactive oxygen species, and nitric oxide (112) (Fig. 2).

Furthermore, the α and β chemokines (produced by glia), which are expressed during the subacute, acute, and chronic stages of HIV-1 infection, may play an important role in trafficking of mononuclear pyocytes within the brain (120). The mechanism by which morphine decreases the secretion of α and β chemokines (important inhibitory cytokines for the expression of HIV) and at the same time increases the expression of chemokine receptors CCR5 and CCR3 (coreceptors for HIV) seems to be mediated by the MOR, as those effects were completely blocked by the additional of

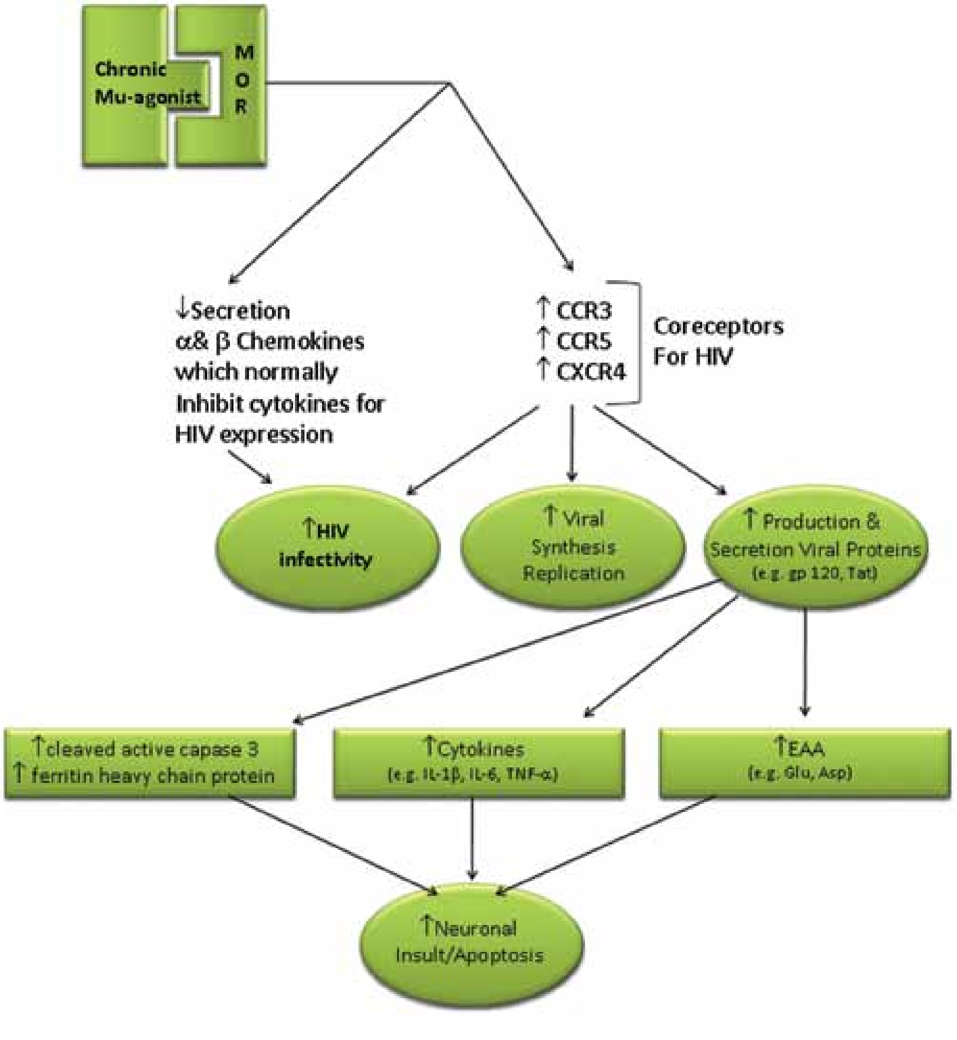

Fig. 2. Schematic of Potential Mechanisms whereby mu-agonists may contribute to promoting HIV infectivity, viral load, and viral-induced painful distal sensory neuropathy

β-fenaprexamine (a selected MOR antagonist) (120). Therefore, MOR is pivotal in mediating the immunomodulatory effects of opioids on astroglia cells of the CNS. (121) Morphine also peripherally regulates the expression of both CCR5 and CCR4 by monocytes and T cells (120).

6.2 Painful HIV-Related Neuropathy May Be Poorly Responsive To Opioids

Koeppe and colleagues (122) performed a cross-sectional cohort study of self-reported pain during 2005 in their HIV clinic. Patients with HIV disease were grouped into 3 cohorts: those receiving daily opioid therapy for chronic pain (cohort 1, n = 115), those with a chronic pain diagnosis but not on daily opioid therapy (cohort 2, n = 209), and those without a chronic pain diagnosis (cohort 3, n = 796). Patients in cohort 1 reported significantly more pain (mean pain scores [0 to 10]: 4.3 cohort 1; 1.9 cohort 2; 0.7 cohort 3), and were more likely to have pain that was of moderate or greater severity (58.6% cohort 1; 15.5% cohort 2; 4.9% cohort 3) (122). They concluded that HIV patients on opioids continued to experience significantly more pain than other patients in their clinic (122). The use of at least short-term opioids and tramadol have been proposed to be among first-line analgesic agents in a stepped care approach to pharmacologic therapy for musculoskeletal symptoms with known cardiovascular disease or risk factors for ischemic heart disease (123).

Opioids may enhance painful HIV-related neuropathy. It is conceivable that opioids, being one of the potentially effective treatments for the amelioration of painful HIV-related neuropathy, may by different effects/mechanisms actually promote nociception in this condition. HIV-induced pathogenesis is exacerbated by opioid abuse. The synergistic neurotoxicity seen appears to be a direct effect of opioids on the CNS. Treatment with morphine may lead to upregulation of the expression of the chemokine receptors CCR3 and CCR5 (124). Additionally, opioids may enhance the cytotoxicity of HIV-1 viral protein gp 120 via mechanisms that involve intracellular calcium modulation with subsequent direct glial effects (124). Although this may be true for morphine, it may not hold true for other opioids. Furthermore, opioids may exhibit pronociceptive actions via binding to glial opioid receptors (125) and/or induce toll-like receptor 3 (TLR4) signaling and facilitating glial activation (126-129); upregulation of TNF, IL-1, and IL-6 in the spinal cord (126-130); upregulation of TNF, IL-1, IL-6 in glia (118); opioid analgesic tolerance, which was temporally correlated with increased glial activation and proinflammatory cytokine production (125, 131).

Wilson et al (132) demonstrated that mRNA expression of the chemokine stromal-derived factor-1 (SDF1/CXCL12) is upregulated following morphine treatment in sensory neurons of the rat. They also showed that there is pronounced CXCR4 expression in satellite glial cells and following morphine treatment, with increased functional CXCR4 expression in sensory neurons of the DRG. Moreover, intraperitoneal administration of the specific CXCR4 antagonist, AMD3100, completely reversed morphine-induced tactile hyperalgesia in the rat. Taken together, the data suggest that opioid induced SDF1/CXCR4 signaling may contribute to the development of long lasting morphine-induced tactile hyperalgesia (132).

Effects of opioids on chemokine receptor expression are potentially important determinants of HIV-1 infection rates among intravenous drug users as the chemokine receptors CCR5 and CXCR4 are coreceptors for the HIV-1 virus coat protein, gp120. Multiple studies using chronic morphine or the selective mu opioid agonist, (D-Ala2, N-MePhe4, Gly-ol)-enkephalin (DAMGO) produce increased expression of monocyte chemoattractant protein-1 (MCP1/CCL2), regulated upon activation normal T cell expressed and secreted (RANTES/CCL5), and their respective receptors, CCR2 and CCR5, in astrocytes and neurons via largely unknown mechanisms (133-135). A similar study demonstrated that DAMGO substantially increased the expression of both CCR5 and CXCR4 in leukocytes (136).

Heinisch et al (137) demonstrated co-expression of MOR-CXCR4 receptors on individual neurons in several regions including cingulate cortex, hippocampus, and PAG, providing anatomic support for potential functional receptor interactions. They found that in the presence of CXCL12, morphine's electrophysiological effects were blocked in all neurons examined, suggesting MOR-CXCR4 heterologous desensitization in the PAG at the single-cell level. These interactions may contribute to the limited utility of opioid analgesics for inflammatory pain treatment and support the notion of chemokines as neuromodulators (137).

6.3 The Interaction Of Opioids and HIV May Have Pronociceptive Effects

Yue and colleagues (138) found that sustained morphine treatment significantly augments intracellular cAMP production as well as basal CGRP release from cultured neonatal rat DRG neurons. The selective PKA inhibitor, H-89, attenuates the sustained morphine-mediated augmentation of basal CGRP release, indicating that the cAMP/PKA pathway plays an important role in regulation of CGRP release from sensory neurons (138). They also demonstrated that selective Raf-1 inhibitor, GW 5074, by inhibiting Raf-1 mediated phosphorylation and sensitization of adenylyl cyclase(s), attenuated both the cAMP overshoot and the augmentation of CGRP release mediated by sustained morphine in neonatal rat DRG neurons (138). Yue et al (138) suggested that their study demonstrates that Raf-1 mediated activation of the cAMP/PKA pathway could be a major intracellular signal transduction pathway involved in the augmentation of pain neurotransmitter release from primary sensory neurons upon sustained opioid analgesic treatment.

Human primary astrocytes exposed to the toxic HIV envelope protein gp120 had a significant increase in TLR4 protein expression (139). Similarly, it appears that certain opioids (e.g., morphine sulfate) may also contribute to a significant increase in TLR4 signaling (140). Conceivably, the combination of opioids and HIV gp 120 may have synergistic effects in promoting TLR4 signaling, glial activation, and pronociception.

Exposure to HIV-1 Tat, gp120, and/or morphine significantly altered the proportion of TLR-immunopositive and/or TLR expression by astroglia in a TLR-specific manner. Subsets of astroglia displayed significant increases in TLR2 with reciprocal decreases in TLR9 expression in response to Tat or gp120 ± morphine treatment (141). Additionally, both HIV-1 Tat and/or gp 120 and/or morphine may promote chemokine signaling glial activation, and pronociception. El-Hage et al (142) studied the effects of morphine and the HIV-1 protein toxin Tat(1-72) on astroglial function. When combined with morphine, Tat causes synergistic increases in Ca(2+)(i). Moreover, astrocyte cultures treated with morphine and Tat showed exaggerated increases in chemokine release, including monocyte chemoattractant protein-1 (MCP-1) and regulated on activation, normal T cell expressed and secreted (RANTES), as well as interleukin-6 (IL-6). Morphine-Tat interactions were prevented by the mu-opioid receptor antagonist beta-funaltrexamine, or by immunoneutralizing Tat(1-72) or substituting a nontoxic, deletion mutant (Tat[Delta31-61]) (142).

CC-chemokine ligand 5, CCL5, also known as RANTES, in particular, attracts and activates mononuclear phagocytes, as well as several other leukocyte types, to sites of injury or infection (143, 144). CCL5 is dramatically increased in the CNS of HIV-infected individuals (145-147). CCL5 preferentially activates its cognate receptor, CCR5, which is a cofactor for HIV entry into cells and can modulate HIV/SIV infectivity in the CNS and elsewhere (148-153). Microglia revealed modest, albeit significant, increases in the proportion of CCL2 positive cells with combined Tat and morphine exposure, suggesting that CCL5 preferentially affects CCL2 expression by astroglia. Thus, it appears that CCL5 mediates glial activation caused by Tat and morphine, thereby aggravating HIV-1 neuropathogenesis (154).

Benamar and colleagues (155) demonstrated that RANTES/CCL5 (0.1–0.4 μg) induces a dose-dependent hyperalgesia when this chemokine is infused directly into the periaqueductal grey (PAG) (155). The onset of action of RANTES/CCL5 was rapid, with significant hyperalgesia observed at 15 minutes post injection. These data show that the activation of RANTES/CCL5 receptors in the PAG can produce pain, and that the PAG plays a role in the regulation of chemokine-induced hyperalgesia (155).

Although Fig. 3 attempts to simplify things, the manner in which cells respond to chemokines is complex because most chemokines bind to more than one receptor and most receptors bind several chemokines (156). RANTES/CCL5 signals through the CC-chemokine receptors CCR1, CCR3, CCR4 and CCR5. In an attempt to confirm that the hyperalgesic effect is indeed due to the action of RANTES/CCL5 in the PAG, Benamar and colleagues (155) tested the effect of the specific antibodies against RANTES/CCL5 on the hyperalgesia induced by RANTES/CCL5. The selective neutralization with specific polyclonal antibodies prevented the hyperalgesic response induced by RANTES/CCL5, indicating that RANTES/CCL5 action represents a specific functional reaction to the presence of this chemokine in this brain area (155).

Smith (157) has proposed that morphine may also synergize with the Tat protein from HIV to promote pronociceptive signaling (Fig. 3). Growth factor receptor-binding protein-2 (Grb2), consisting of 3 domains, 2 SH3 and a single SH2 domain, is one of the key factors in the Rasand Raf signaling cascades (Rom 2011) This is not a proper citation. The only Rom in the references list is #163, which would also make this citation out of order. The trans-activating factor Tat is an 86–101 amino acid polypeptide encoded by the HIV-1 virus (158). Several studies have demonstrated the importance of HIV-1 Tat in the viral replication cycle and in the pathogenesis of AIDS (159, 160). Similar to another HIV protein, Nef (161), Tat also contains proline-rich motives which are putative SH3-binding domains, one at the N-terminal and the other at the C-terminus of the protein. Grb2 is a ubiquitously expressed adaptor protein that has mitogenic properties and is required for several basic cellular processes (162). It can interact with tyrosine phosphorylated substrates, such as tyrosine kinase receptors, via the SH2 domain and with a variety of other signaling molecules via the 2 SH3 domains. Rom and colleagues (163) provided evidence for Tat/Grb2 direct interaction, which is mediated by the SH3 C-terminal domain of Grb2 and polyproline regions of Tat. This interaction is functional and bidirectional: it affects cellular pathways as well as viral replication.

Furthermore, a unique interaction, seen in Fig. 3, which may be a potential specific target to develop a specific antinociceptive agent, is the interaction of HIV Tat and Grb2 of the human cell. Specific agents interfering in this Tat/Grb2 interaction may have clinically meaningful antinociceptive properties. Additionally, Raf-1 inhibitors, PKA inhibitors, and chemokine inhibitors may exhibit useful antinociceptive properties for HIV-related DSP.

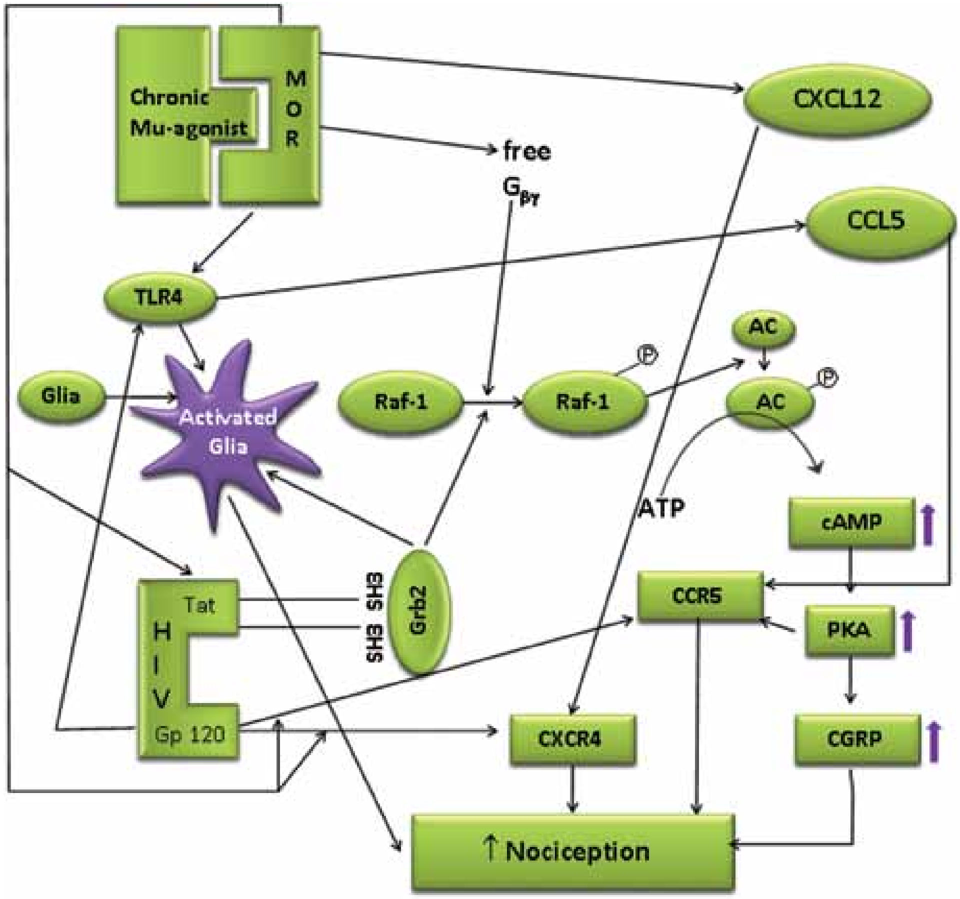

Fig. 3. *Schematic of Potential Mechanisms whereby mu-agonists may contribute to promoting HIV-related pain*

Chen et al (164) demonstrated that the analgesic activity of morphine can be reduced by the presence of gp120 in the PAG and that pretreatment with AMD3100 (a CXCR4 antagonist) is able to restore the analgesic effects of morphine (164).

Finally, not unexpectedly, all opioids are not created equally. A lack of interaction between buprenorphine and the immune system has been reported previously. Administration of buprenorphine (in contrast to morphine) to the PAG of rats elicited no functional changes in splenic natural killer cells, T-lymphocytes or macrophages (165). Additionally, several preclinical studies clearly indicate that buprenorphine does not possess immunosuppressive properties (165-168). Also, with respect to analgesia, although HIV-gp120 may function to significantly diminish morphine and methadone-induced antinociception, it appears that buprenorphine-induced antinociception was essentially unaffected by gp120, and may be acting via different mechanisms (169).

The presence of SDF-1α/CXCL12 in the PAG differentially alters the antinociceptive function of opioid medications. While it was able to diminish the antinociception induced by morphine (170), direct infusion of SDF-1α/CXCL12 into the PAG did not affect the buprenorphine-induced antinociception. Buprenorphine appears to be more effective in the presence of high levels of SDF-1α/CXCL12 in the brain (which may occur during neuro-inflammatory conditions) (171).

It is conceivable that buprenorphine may be a more effective analgesic than an equianalgesic dose of methadone in the presence of gp120 in the brain, a condition that is associated with HIV-related pain and infection (Palma 2011). Thus, buprenorphine should be considered as a potential option for clinicians who are about to initiate or rotate chronic opioid therapy for patients with advanced HIV-associated pain neuropathy.

7.0 Conclusion

Preclinical evidence suggests a complex interplay of many mediators and signaling cascades may be involved in the initiation and/or maintenance of HIV-related DSP (Fig. 1). It is conceivable that some of the very agents which are used to treat HIV infection/disease (e.g., NRTIs) as well as the associated pain of HIV-related painful DSP (e.g., opioids) may actually facilitate pronociceptive processes involved in contributing to HIV-related DSP pain. It thus appears conceivable that the use of at least certain opioids in efforts to achieve analgesia in patients with painful HIV-related neuropathy may be less than ideal since at least certain opioid analgesics themselves may potentially contribute to "fueling the fire" of HIV enhanced pain hypersensitivity, at least in part via upregulation of specific chemokine receptors (e.g. CXCR4) which seem to be vitally important in promoting HIV-related pain facilitation. If opioids exhibit pronociceptive actions in the setting of HIV-related painful DSP, then it would seem prudent to at least reserve these analgesic agents as either second-line or perhaps more appropriately third-line considerations as treatment choices for this challenging neuropathic pain syndrome. Clinicians should carefully weigh the risk/benefit ratio before initiating chronic opioid therapy for HIV-related painful DSP. In addition to existing broad spectrum analgesics, a multitude of future potential analgesic targets may exist which may yield improved analgesia with more favorable side effect profiles.

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