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ORIGINAL PAPER

Scaling Synapses in the Presence of HIV

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Abstract
A defining feature of HIV-associated neurocognitive disorder (HAND) is the loss of excitatory synaptic connections. Synaptic changes that occur during exposure to HIV appear to result, in part, from a homeostatic scaling response. Here we discuss the mechanisms of these changes from the perspective that they might be part of a coping mechanism that reduces synapses to prevent excitotoxicity. In transgenic animals expressing the HIV proteins Tat or gp120, the loss of synaptic markers precedes changes in neuronal number. In vitro studies have shown that HIV-induced synapse loss and cell death are mediated by distinct mechanisms. Both in vitro and animal studies suggest that HIV-induced synaptic scaling engages new mechanisms that suppress network connectivity and that these processes might be amenable to therapeutic intervention. Indeed, pharmacological reversal of synapse loss induced by HIV Tat restores cognitive function. In summary, studies indicate that there are temporal, mechanistic and pharmacological features of HIV-induced synapse loss that are consistent with homeostatic plasticity. The increasingly well delineated signaling mechanisms that regulate synaptic scaling may reveal pharmacological targets suitable for normalizing synaptic function in chronic neuroinflammatory states such as HAND.

Keywords HIV-1 · Homeostatic plasticity · NMDA receptor · Synaptic scaling · HIV-associated neurocognitive disorder

Introduction

HIV-associated neurocognitive disorder (HAND) afflicts almost half of HIV-infected individuals [1]. Cognitive deficits in HAND correlate with the loss of synaptic connections [2–4] and patients with mild neurocognitive impairment have an increased risk of further cognitive decline [5]. Because HIV does not infect neurons, HIV neurotoxicity is indirect and thought to be mediated by a neuroinflammatory response to viral proteins and inflammatory cytokines released by infected microglia and macrophages [1, 5, 6]. Here we discuss the effects of HIV neurotoxins on synaptic function and evidence that suggests early stage synapse loss might result from homeostatic plasticity.

Mechanism of Synapse Loss

Neurons scale their synaptic input in response to both low and high levels of activity [7]. Whether these same processes are responsible for the synapse loss observed during neurodegenerative conditions remains unclear. A dying cell will retract dendrites and lose network connections leading to overt synapse loss. In contrast, homeostatic scaling is a neurophysiological process that neurons use to stabilize their activity around a functional operating point. In the early stages of HAND, synapse loss precedes overt neuronal death by months to years [8], suggesting that synaptic changes may be a coping mechanism. The viral proteins and inflammatory cytokines elevated by HIV in the brain result in excessive activation of receptors for the neurotransmitter glutamate. Homeostatic scaling down of glutamatergic synapses under excitotoxic conditions may be a neuroprotective response, rather than a symptom of the overt synapse loss that accompanies a cell's demise. Furthermore, this type of scaling may be reversible during the early stages of the disease. This homeostatic plasticity model posits that HIV tips the precarious balance neurons maintain between full integration into synaptic networks and the risk of excitotoxicity (Fig. 1).

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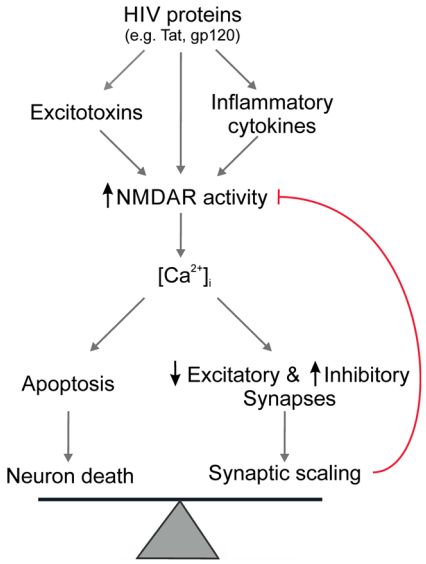

Fig. 1 Balancing survival and function. Neurotoxic factors elevated by HIV act via various upstream mechanisms to converge on the potentiation of NMDARs. Neurons and networks then adapt to the presence of this stimulus by scaling synapses to attenuate Ca^{2+}-mediated toxicity

Neuroinflammation is a contributing factor to synapse loss in many neurodegenerative diseases [9–11]. In the context of the neuroinflammatory response in HAND, key factors include secretion of inflammatory cytokines, release of HIV proteins, activation of glia, and release of reactive oxygen species. Inflammatory cytokines are elevated in the CSF of HIV patients with cognitive impairment [12, 13]. Synapse loss induced by cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) has been described in a number of models and has been the subject of thorough reviews [14, 15]. Reactive oxygen species impair synaptic function [14] and are released following exposure to HIV proteins and antiretroviral drugs [15–18]. However, in the context of HIV, reactive oxygen species have been linked to cell death [19, 20] but their role in synapse loss has not been explored.

Exposure to the HIV envelope glycoprotein gp120 and the HIV protein Tat (transactivator of transcription) produces synapse loss both in vitro and in animal models [21–25]. Several observations are consistent with the idea that these synaptic changes might be part of a neuroprotective scaling response. The synapse loss induced by HIV proteins occurs prior to cell death in in vitro studies [21, 24, 26, 27] and in transgenic animals expressing Tat or gp120 the loss of synaptic markers precedes changes in neuronal number [23, 28–30]. Pharmacological reversal of synapse loss induced by the HIV protein Tat is consistent with the idea that synaptic changes may result from homeostatic plasticity [21, 31, 32]. Indeed, different mechanisms are responsible for HIV Tat-induced synapse loss and cell death; cell death can be prevented without affecting synapse loss and preventing synapse loss actually sensitizes neurons to cell death [21].

Both cell death and synaptic changes are initiated by over activation of NMDARs, but the downstream signaling pathways diverge to produce distinct outcomes [6, 33] (Fig. 2). HIV proteins and inflammatory cytokines produce a rapid initial potentiation of NMDAR activity [34–37]. High concentrations of HIV Tat (> 1 μM) act directly on NMDARs to increase activity [38], lower concentrations more subtly potentiate NMDAR function through kinase signaling cascades including the Src [39] and protein kinase C [35] pathways. Exposure to $gp120_{IIIB}$ potentiates NMDARs via protein kinase A dependent phosphorylation [40] and Src activation [36, 41, 42]. It appears that phosphorylation-mediated potentiation of the NMDAR is a common step that initiates synaptic changes (Fig. 2), consistent with protection of synapses afforded by NMDAR antagonists [21, 24, 31]. This initial over activation of NMDARs is followed by down regulation [43–45] and loss of excitatory synapses [21–24].

NMDAR subtypes play specific roles in the Tat-induced loss of synapses connecting hippocampal neurons in culture. NMDARs are tetramers composed of two obligatory GluN1 subunits and two GluN2 (A–D) or GluN3 (A–B) subunits. The predominant GluN2 subtypes in the hippocampus are GluN2A and GluN2B [46]. Activation of GluN2A-containing NMDARs promotes neuronal survival, whereas activation of GluN2B-containing NMDARs can activate pro-apoptotic pathways [47, 48]. Inhibition of GluN2A, but not GluN2B-containing NMDARs prevents Tat-induced synapse loss which is consistent with the pro-survival role of GluN2A-containing NMDARs, because early synapse loss appears to be a homeostatic mechanism to prevent cell death. Furthermore, inhibition of GluN2B, but not GluN2A-containing NMDARs prevents Tat-induced cell death [31]. Application of an inhibitor selective for GluN2B-containing NMDARs after synapse loss has already occurred restores synaptic density. Thus, the pharmacology changes during exposure to the HIV neurotoxin such that the sustained activation of GluN2B-containing NMDARs prevents recovery of synapses. Several factors may contribute to the selective roles of NMDAR subtypes. Cellular location may account for some specificity; GluN2A-containing NMDARs are predominantly synaptic and their activation is pro-survival, whereas GluN2B-containing NMDARs are predominantly extrasynaptic and their activation is pro-apoptotic [47, 49]. Another distinction between the GluN2 subtypes is their intracellular C-terminal domains which couple to different downstream signaling pathways [50]. Thus, the processes activated by Ca^{2+} influx via NMDARs display a source specificity.

Pathological activation of NMDARs produces excessive Na^+ and Ca^{2+} influx that elicits toxicity via mitochondrial

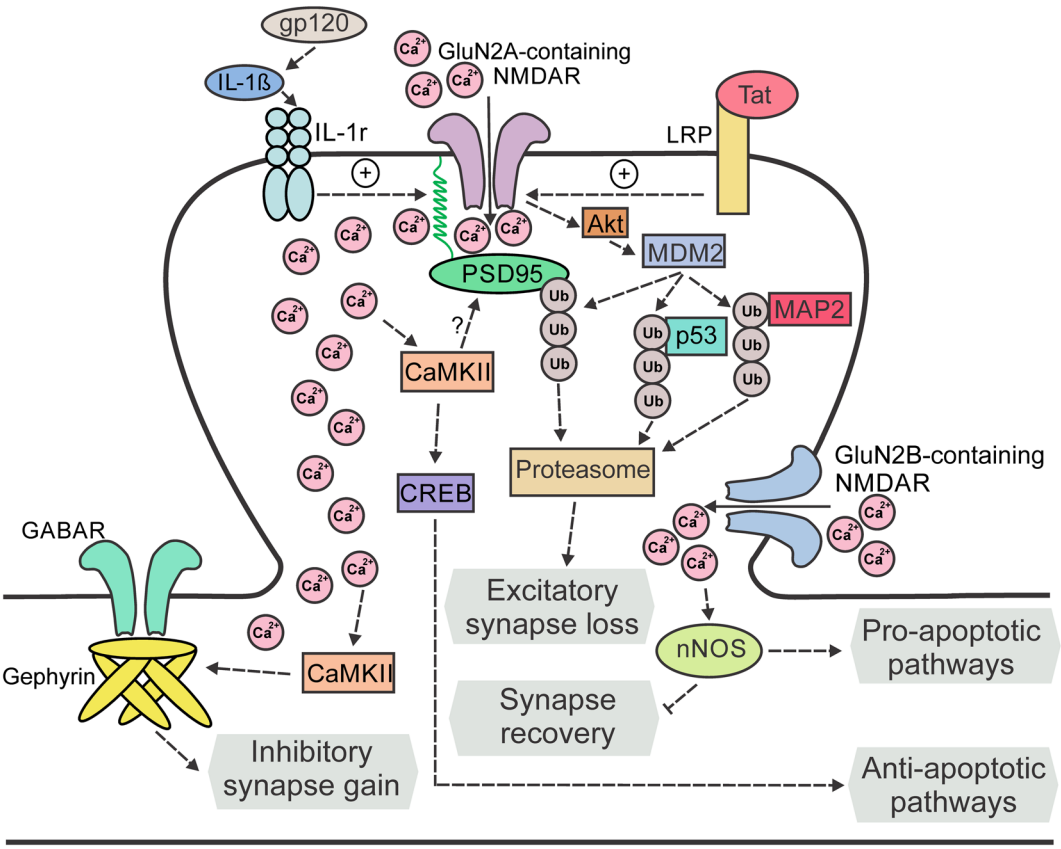

Fig. 2 HIV neurotoxins potentiate NMDARs to evoke distinct synaptic scaling and neuronal death pathways. GluN2A-containing NMDARs promote anti-apoptotic pathways and regulate changes to excitatory and inhibitory synapses. GluN2B-containing NMDARs promote pro-apoptotic pathways and prevent synapse recovery. Figure modified from [60]

generated reactive oxygen species [51], dendritic swelling [52], and activation of the pro-apoptotic caspase cascade [53]. In addition to NMDAR, HIV proteins potentiate other Ca^{2+} permeable channels including L type calcium channels, TRPC channels, and ryanodine- and IP3-receptor Ca^{2+} release channels [33]. These channels have not been linked directly to HIV induced synaptic changes, although their effects on Ca^{2+}-mediated changes in metabolism, neurotransmitter release and network excitability could indirectly affect NMDAR signaling. HIV also affects gap junctions and hemi-channels [54]. Recent studies have shown metabotropic NMDAR activity is important for regulating pannexin 1 gap junctions [55], excitotoxicity [56] and synaptic plasticity [57]. Proteomic analysis of synaptosomes derived from HIV infected individuals found synapsin Ib levels were inversely related to HIV-1 loads [58]. Loss of this presynaptic marker could be a form of scaling, which in vitro studies indicate is dependent on NMDARs situated on the postsynaptic dendrite [59]. Experiments using chelators with different Ca^{2+} binding kinetics suggest that the Ca^{2+}-sensitive target that drives loss of glutamatergic synapses following exposure to HIV Tat is close to the mouth of the NMDA-gated channel [60].

Ca^{2+} entry through the NMDAR can activate a number of signaling pathways that modulate synaptic function [7, 61]. Calmodulin-dependent kinase II (CamKII) is localized in close proximity to the mouth of the NMDAR [62, 63]. Ca^{2+} binding to calmodulin with subsequent activation of CamKII is a key pathway regulating synaptic plasticity, including induction of LTP through phosphorylation of AMPA receptors and changes in gene expression following activation of CREB [64–66]. Indeed, inhibition of CamKII prevents Tat-induced synapse loss [60]. Additionally, NMDAR activation and HIV gp120 upregulate matrix metalloprotease-2 (MMP-2), an enzyme that breaks down the extracellular matrix to facilitate spine remodeling [67, 68]. Down regulation of synaptic strength is linked to NMDA-dependent activation of calcineurin [69]. However, inhibition of this Ca^{2+}-sensitive phosphatase with FK506 failed to prevent changes in synapse number evoked by HIV Tat [60], suggesting that the death-associated protein kinase pathway is not responsible for the initial loss of synapses. Ca^{2+} entry via NMDARs,

particularly during synaptic activity, induces robust activation of CREB and its co-activator CREB-binding protein, resulting in the transcription of many pro-survival genes [70], including Brain-derived neurotrophic factor (BDNF).

BDNF is a growth factor secreted by excitatory neurons; depending the specific brain region it can modulate synaptic upscaling and downscaling [71, 72]. gp120 decreases furin levels reducing pro-BDNF processing, which is consistent with BDNF levels in tissue from postmortem HIV-positive subjects [73]. Both gp120 and TNF-α reduce anterograde transport and intracellular stores of BDNF [74]. Additionally, Tat induced microRNA-132 expression down-regulates a number of genes, including BDNF [75]. In patients with HAND, CSF levels of BDNF and fibroblast growth factor 2 (FGF2) are lower than control patients [76] and the severity of neurological disease correlates with BDNF and neurotrophin-3 in the CSF [77]. Whether reduced BDNF levels in HAND result from a decrease in the number of excitatory synapses in impaired patients or whether reduced BDNF is a result of HIV neurotoxins disrupting normal BDNF processing is unclear. Either scenario implies strategies that correct BDNF levels might restore synaptic function.

GluN2A-containing NMDARs can activate the kinase Akt to promote neuronal survival [47, 56]. Tat activates Akt [68] and Akt is necessary for Tat-induced downregulation of NMDAR activity [43]. Mass spectrometry quantification of synaptic proteins in brains from HIV gp120 transgenic mice and human HAND patients found lowered pAkt/Akt ratio consistent with dysregulation of this pathway [78]. Tat-activated Akt phosphorylates the E3 ligase MDM2 (murine double minute 2), increasing its activity [79]. Inhibition of MDM2 prevents both Tat and gp120-induced synapse loss [21, 24]. MDM2 plays a key role in activity dependent homeostatic plasticity [80], consistent with the idea that fundamental scaling mechanisms are recruited during HIV neurotoxicity. Changes in proteasome subunit composition correlate with HIV loads in brain tissue, further implicating changes in protein turnover as a contributing factor to HAND [81]. MDM2 ubiquitinates many target proteins including p53, MAP2 and PSD-95 [82–84]. PSD-95 is a scaffolding protein that tethers excitatory receptors such as NMDARs and AMPARs to the post-synaptic membrane. Mutation of the PEST sequence at the N terminus of PSD-95, a site that regulates its stability and ubiquitination [85], prevents Tat-induced synapse loss [21]. Because PSD-95 stabilizes spines, its ubiquitination by MDM2 may lead to retraction of the spine and synapse loss [82]. Indeed, knockdown of the MAGUK family of scaffolding proteins, which includes PSD-95, produces a synaptic consolidation similar to the homeostatic process evoked by HIV proteins [86]. Tat also causes a proteasome-mediated degradation of MAP2 and the collapse of cytoskeletal filaments [84]. Indeed, MAP2 levels are reduced in SIV models [87] and MAP2-positive neurons are selectively vulnerable in HIV patients [88]. p53, another target of MDM2, regulates transcription which may affect synapse density by changing the expression of synaptic proteins, such as ephrin B2 [89], a receptor involved in the formation of glutamatergic synapses that is reduced in postmortem brains of HIV-infected subjects [90]. However, p53 levels were elevated in an SIV model [91]. The lower pAkt/Akt ratio and elevated p53 levels observed in models with chronic exposure to virus or toxins may result from measurements taken at a later stage of the disease. In summary, the MDM2 pathway provides a clear example of a signaling cascade activated by the increase in NMDAR activity induced by HIV neurotoxins and leads to downscaling of glutamatergic synapses.

Changes in the release or reuptake of glutamate produced by HIV may also contribute to the over activation of NMDARs responsible for synapse loss. Indeed, CSF glutamate levels correlate with cognitive decline in HIV-infected patients [92]. During SIV infection excitatory amino acid transporters (EAATs) are disrupted [93]. The HIV proteins Tat and gp120 reduce expression of EAAT2 in astrocytes, reducing uptake of glutamate [94–97]. TNFα, a pro-inflammatory cytokine produced by HIV infected macrophages and microglia, inhibits glutamate uptake into primary human astrocytes [98]. Thus, multiple mechanisms activated by HIV in the brain lead to impaired glutamate uptake. HIV proteins also increase the release of glutamate. HIV proteins evoke the release of cytokines, such as IL-1β, which increase the production of prostaglandins that act presynaptically to increase glutamate release [99]. Similarly, platelet-activating factor, which is elevated in inflammatory conditions such as HIV-associated dementia (HAD), produces synaptic facilitation and sensitization to dendritic damage by increasing glutamate release [100–102]. Tat also acts directly on presynaptic terminals to increase glutamate release [103, 104]. The phosphorylation of tyrosines on the NMDAR induced by HIV proteins and inflammatory cytokines does not activate it directly, phosphorylation sensitizes NMDARs to glutamate [105]. Thus, elevated extracellular glutamate synergizes with the increased sensitivity of the receptor likely contributing to the altered network activity observed in the presence of HIV [106–109]. Networks adapt to altered activity levels through homeostatic scaling mechanisms. Thus, synaptic scaling may be an attempt to normalize activity levels in networks that have been excited by persistent elevation of extracellular glutamate due to the presence of HIV.

Many HAND patients exhibit movement disorders and sub-cortical pathology consistent with abnormal dopaminergic synaptic markers in striatal extracts from patients with HIV encephalitis (HIVE) [110]. Tat decreases dopamine (DA) transporter expression and function and also inhibits the vesicular monoamine transporter [111–114]. Impaired DA transport may elevate DA levels early in infection possibly leading to

DA induced toxicity apparent at later stages of disease [115]. Changes in DA metabolism may account for some of the pronounced adverse effects produced by drugs of abuse in HAND patients [116]. While HAND neuropathology includes the loss of dopaminergic synapses this loss appears to result from a degenerative process, possibly resulting from oxidative damage produced by excess DA. Elevated DA levels may affect the plasticity of glutamatergic and GABAergic synapses, although the degree to which these neurotransmitter systems interact to scale synapses in HIV is unclear.

Activation of microglia is a key feature of HAND [117]. Contact with microglial filopodia is an early step in synapse elimination following injection of HIV Tat protein into the CNS [118, 119]. Recent studies have shown that microglia use complement-based tagging to prune synapses during development [120] and neurodegenerative disease [121]. Microglial mediated synaptic pruning occurs in animal models of HAND [122] and the level of complement factors (C1q/C3) detected in the CSF of HIV infected individuals correlates with a marker for neuronal damage [123]. However, the phagocytic ability of monocytes and macrophages [124, 125] is decreased following HIV infection or exposure to Tat [126]. Thus, the role of synaptic pruning by microglia in HIV-induced synapse loss is unclear, although its participation in refining neural circuits during development would seem to indicate that this process may be regulated by synaptic activity. The degree to which microglia contribute to the removal of synaptic structures will influence whether recovery of synaptic density involves the formation of new synapses.

In summary, while some studies indicate that synapse loss induced by HIV is part of the agonal event, other results, particularly from models in which discrete application of HIV neurotoxins mimic the early phase of infection, appear to support a mechanism more similar to homeostatic scaling. Scaling normalizes cellular excitability and balances network activity so that information encoded in synaptic connections is maintained without saturating the dynamic range of the network or inducing excitotoxicity. Thus, homeostatic scaling mechanisms may participate in adaptation to the presence of HIV neurotoxins. Mapping these neurophysiological mechanisms to the pathological neuroinflammatory state produced by HIV in the brain may inform the development of therapeutic approaches to prevent or correct this overcompensation.

Increased Inhibition to Counter HIV-Induced Excitotoxicity

Network scaling in response to excess excitation increases GABAergic tone in addition to decreasing glutamatergic activity. Increased number of inhibitory synapses or levels of gephyrin, a scaffolding protein found at GABAergic synapses, have been observed in hippocampal cultures treated with Tat protein and in CA1 hippocampal neurons from mice expressing HIV Tat [30, 60]. The formation of new inhibitory synapses is more consistent with a coping mechanism than part of the death process. The increase in the number of inhibitory synapses during exposure to HIV neurotoxins follows a time course similar to the loss of excitatory synapses and the adaptation of NMDA receptors [21, 127]. Like the loss of excitatory synapses, the increase in inhibitory synapses is initiated by Ca^{2+} influx through GluN2A-containing NMDA receptors and subsequent activation of CaMKII [21, 24, 60] (Fig. 2). Increased excitatory neurotransmission can activate Npas4 which increases the expression of genes that control inhibitory synapse development [128], although whether this homeostatic process participates in network adaptation to HIV neurotoxins is not known. Thus, increased inhibitory synaptic transmission is part of a neuroprotective pathway distinct from that regulating glutamatergic synapses. However, in striatum and prefrontal cortex exposed to HIV proteins GABAergic neurotransmission is inhibited [129, 130]. The same Tat expressing transgenic mice that exhibited increased gephyrin immunostaining in the hippocampus, also exhibited decreased levels of synaptotagmin 2, a marker for GABAergic presynaptic terminals [30]. GABA-A receptors are down-regulated in frontal neocortex from patients with HIV encephalitis [131]. The reason for the increased GABAergic signaling in some HIV models and decreased signaling in others is unclear but, might result from synaptic adaptations that are unique to specific brain regions, the use of different methods for detecting inhibitory synapses, and the timing of the measurement with early detection favoring scaling mechanisms and later stages of disease showing loss of synapses and neurons. There is precedent in other neurodegenerative disorders that GABAergic over compensation leads to impaired function. Excessive inhibition creates an excitatory-inhibitory imbalance that impairs cognitive function in Down syndrome [132–134]. Increased tonic inhibition impairs memory in an Alzheimer's disease model [135]. Inhibition of GABA transporters, a target of some antiepileptic drugs, produces cognitive deficits [136]. Whether excess inhibition contributes to cognitive impairment in HAND is not known.

Preventing HIV Neurotoxicity

The recognition that loss of synaptic connections underlies neurologic disease in HIV infected patients brought the synapse to the forefront as a target for neuroprotective strategies in HAND [8]. Rather than review the many compounds tested for neuroprotective effects in models of HAND, we focus on several drugs that highlight the types of

mechanisms that can be modulated to prevent or normalize synaptic scaling. These include NMDA receptors, microglia-mediated inflammatory processes, neurotrophic growth factors, and the neuroprotective endocannabinoid system.

NMDA receptors play a major role in pathological neuronal excitation, and based on the results that have been discussed, NMDAR antagonism may attenuate HIV neuropathological processes. Memantine is an uncompetitive blocker of NMDA-gated channels, which preferentially inhibits extrasynaptic NMDARs because of its fast off-rate [137]. In vitro and in vivo studies with memantine have demonstrated protective effects against neurotoxicity evoked by HIV gp120 and Tat [138–140]. The NMDAR antagonist dizocilpine protects against HIV protein-induced synapse loss and death in vitro [31]. While the use of broad spectrum glutamate receptor antagonists in patients is fraught with adverse effects [141, 142], drugs targeting NMDAR subtypes, particularly those that contain the GluN2B subunit, show promise in animal models of HAND [32].

Microglia involvement in HIV-related neurotoxicity includes synaptic pruning and release of cytokines, chemokines, prostaglandins, and nitric oxide [117]. Anti-inflammatory drugs are an increasingly attractive adjunctive therapy for the treatment of HAND. Minocycline is a broad-spectrum tetracycline antibiotic derivative that is neuroprotective in models of neurodegenerative disease [143–145]. Minocycline inhibits HIV production in infected microglial cultures without being toxic to microglia themselves [146] and minocycline-treated macaques showed less severe encephalitis, reduced CNS expression of neuroinflammatory markers, less axonal degeneration, and lower CNS virus replication [147]. These promising results did not translate in clinical trials of minocycline for the treatment of HAND [148, 149], despite being safe and well-tolerated among subjects. This discrepancy between the effects of minocycline in the SIV encephalitis model and HIV-positive individuals warrants further studies to define the precise underlying neuroprotective mechanism in the former in order to facilitate development of more efficacious therapeutics for HAND. Drugs that suppress the function of microglia act upstream of NMDAR potentiation to prevent the excitation that subsequently engages homeostatic processes.

Levels of neurotrophic factors are suppressed in HIV neurotoxicity models and HAND patients (Section "Mechanism of Synapse Loss"). Replacing this deficit with exogenous neurotrophins increases neuronal survival and normalizes synaptic connections [150]. FGF1 protected primary human cultures from HIV gp120 [151] and overexpression of FGF1 prevented neurodegeneration in gp120 expressing transgenic mice [152]. BDNF is neuroprotective against gp120 in vitro and in vivo [153]. Normalizing neurotrophin levels demonstrates the utility of modulating the mechanisms responsible for synaptic scaling.

The endocannabinoid (eCB) system provides on demand protection from excitotoxicity and neuroinflammation [154–157]. Cannabinoid type 1 receptors (CB_1R) are expressed in neurons and modulate synaptic transmission. CB_2R are primarily expressed in cells of the immune system and modulate inflammation. CB_2R agonists are neuroprotective in several models of HIV neurotoxicity [158]. CB_2R agonists protect synaptic networks from gp120 by inhibiting release of inflammatory cytokines from microglia [24] and they restore suppressed neurogenesis in gp120 transgenic mice [159]. In a mouse model of HIVE a CB_2R agonist reduced the levels of immune activation, infiltration of human cells into the brain, and downregulated neuroinflammation [160]. Impaired function of the eCB system may disrupt its neuroprotective capability; thus, upregulating this system may attenuate HIV neurotoxicity. Inhibition of the 2-arachidonyl glycerol (2-AG) hydrolytic enzyme monoacylglycerol lipase (MGL) by the selective, irreversible inhibitor JZL184 prevents gp120-induced synapse loss [42]. Inhibition of MGL by JZL184 has also been demonstrated to suppress proinflammatory cascades that underlie neurodegenerative disorders, as demonstrated in an MPTP mouse model of Parkinson's disease [161]. Because inhibition of MGL only potentiates endogenously produced 2-AG, receptor activation is dependent on a stimulus, enabling prolonged, low-dose MGL inhibition to elicit an anti-inflammatory effect without producing CB_1R tolerance or cannabinoid dependence [162]. Furthermore, because brain arachidonic acid production is primarily dependent on MGL, in contrast to the gut, drugs that inhibit MGL can reduce brain prostaglandin levels without the gastrointestinal side effects produced by nonsteroidal anti-inflammatory drugs [163]. Thus, MGL inhibition increases 2-AG levels and reduces prostaglandin production to reduce HIV-induced excitotoxicity and neuroinflammation.

Reversing Synapse Loss and Recovering Function

The idea that synaptic changes early in the course of HAND might result from homeostatic scaling to adapt to the presence of HIV neurotoxins is supported by results demonstrating that these changes are reversible. Upon initiation of cART, HIV infected patients with neurocognitive impairment exhibit longitudinal improvement in neuropsychological function and regression of neuropathology [164, 165]. These studies suggest that HAND, at least in part, can be reversed. More recent work has focused on reversing the synaptic deficits in HAND patients in which viral titer is suppressed by cART.

In vitro synaptic networks exposed to HIV toxins initially display an excitotoxic state characterized by potentiated

NMDAR activity, followed by compensatory decreases in the number of excitatory synapses and increases in the number of inhibitory synapses (see Sections "Mechanism of Synapse Loss and Increased Inhibition to Counter HIV-Induced Excitotoxicity"). Generally, manipulations that block the initial excitatory state (see Section "Preventing HIV Neurotoxicity") are distinctly different from treatments that restore synaptic function. One treatment that both prevents and reverses synapse loss is receptor associated protein (RAP), a chaperone protein that binds to the lipoprotein related protein (LRP). Polymorphisms in the genes for LRP, and its ligands apolipoprotein E and α-macroglobulin are linked to Alzheimer's disease [166] and HAD [167]. RAP prevents Tat internalization [168] preventing potentiation of the NMDAR and subsequent loss of synapses [21]. Intriguingly, RAP also rescues lost synapses following Tat exposure, suggesting an LRP-dependent mechanism may be involved in Tat-induced spine suppression [21]. Note that most treatments that attenuate synapse loss evoked by HIV neurotoxins are not able to induce recovery once loss has occurred, consistent with the idea that a new state has developed in which the synaptic network has adapted to the presence of the excitotoxin, changing the pharmacology. For example, excitatory signaling through GluN2A-containing NMDARs plays a critical role in spine loss as indicated by block by the GluN2A antagonists TCN201 and NVP-AAM077 [31, 43]. In contrast, ifenprodil and memantine, antagonists of GluN2B-containing NMDARs, do not block the initial effects of Tat. However, following synapse loss (16–24 h Tat exposure) these drugs rescue synapses [31]. This finding suggests that Tat-exposure may alter synapse regulation such that GluN2B-containing NMDARs are negatively coupled to spine regulation. Collectively these in vitro findings suggest that HIV toxins induce an excitotoxic state that drives synaptic scaling and that reversing these adaptations may be a viable approach to restore cognitive function in HAND.

Despite variability in animal models of HAND, in vivo work suggests that there are potential treatment targets for HIV neurotoxicity, such as K^+ channels, estrogen receptors, and NMDARs. In a HIVE model where immunosuppressed SCID mice were injected with HIV-infected primary human macrophages, the K^+ channel blocker 4-aminopyrdine (4-AP) ameliorated HIVE-associated deficits in long-term potentiation, changes in synaptic structure, and improved spatial learning and memory assessed by radial arm maze [169]. Another study targeted estrogen receptors with the legume isoflavone daidzein and the liquorice extract liquiritigenin, which both act as estrogen receptor agonists [27]. They found that these compounds reversed HIV-Tat induced loss of F-actin labeled puncta, a marker for synaptic spines, but did not assess effects on cognition. Nakanishi and colleagues [170] examined the effects of blocking NMDARs on neuropathology in gp120-expressing mice and reported that the NMDA antagonist nitromemantine reversed both dendritic damage assessed with MAP2 immunoreactivity and loss of presynaptic terminals assessed by synaptophysin immunoreactivity [170]. In an SIV model, treatment with memantine upregulated BDNF and diminished dopamine deficits [171]. Further, our lab has recently used within-subject multiphoton imaging to demonstrate that HIV-1 Tat infusion decreases dendritic spine density, as well as cognitive function in mice, and that administration of ifenprodil, a selective antagonist for GluN2B-containing NMDARs, rescues both dendritic spine density and cognitive function (Fig. 3). These findings collectively suggest that small molecule pharmacotherapy can restore lost synapses and function in HAND, supporting the idea that the initial cognitive deficits resulting from HIV exposure may be due to aberrant homeostatic scaling mechanisms that are potentially controllable.

One of the first clinical trials for HAND treatment used the voltage-gated calcium channel blocker nimodipine [172]. No effects on cognition were reported although, this early trial was conducted against a very different treatment backdrop than that of the current cART era [173], and faced a clinical population with worsened neurocognitive outlook. Later trials have focused on the NMDA antagonist memantine, which has shown some promise in ameliorating Alzheimer's disease symptoms [174]. An initial study administered

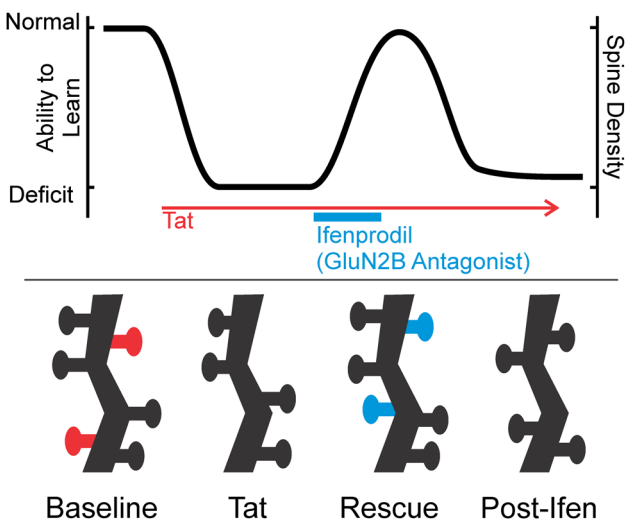

Fig. 3 Synaptic loss and cognitive impairment induced by HIV proteins can be pharmacologically reversed. Infusion of HIV Tat into the lateral ventricle decreased spine density in the retrosplenial cortex and impaired cognitive function. A single infusion of Tat produced a prolonged decrease in spines (horizontal red arrow). Spines lost during Tat exposure are shown in red at baseline. Systemic administration of ifenprodil (blue horizontal bar) rescued spines (new spines are blue) and cognitive function. Note that after clearance of ifenprodil spine density and cognitive function returned to levels observed before drug administration. Figure modified from [32]

memantine to subjects with stage one AIDS dementia complex, within the Adult AIDS Clinical Trial Group (AACTG) [175]. Unfortunately they found no significant effect of memantine on the NPZ-8 neuropsychological index, but did report a promising trend in some clinical subgroups, as well as marked variability. The fact that memantine, an NMDA antagonist, is well tolerated and shows trends towards amelioration of HAND symptoms is promising in light of recent preclinical findings with selective NMDAR targeting drugs, such as those acting on GluN2b-containing NMDARs and negative allosteric modulators. Overall, these reports highlight the challenges facing clinical trials for treatment of progressive disease states; future efforts will need to pay particular attention to disease progression, intervention timing, and treatment duration to demonstrate effectiveness of HAND treatments.

Synthesis and Conclusions

Synaptic changes that occur during exposure to HIV have a component that appears to result from a homeostatic scaling response. HIV-induced synaptic changes share common mechanisms with this form of plasticity. Synaptic scaling is most readily apparent in in vitro studies where the toxicity is evoked by an acute challenge and a clear reversal of HIV induced synaptic damage can be demonstrated. Interestingly, the over activation of NMDARs drives both the early reversible synaptic changes and delayed cell death processes, though these signaling pathways diverge and may be triggered by different subtypes of NMDARs. More slowly developing toxicity accurately reflects the chronic nature of HAND, but in these models it is more difficult to differentiate an early plastic response from the agonal event. cART improves the neurocognitive function in patients beginning treatment, suggesting an initial synaptic resilience, but reversing cognitive impairment in clinical trials has not been encouraging. In vitro and animal studies suggest that following HIV-induced synaptic scaling new mechanisms suppress network connectivity that might be amenable to therapy.

Future Directions

There is currently no effective treatment for HAND. The idea that HIV-induced synapse loss is due, at least in part, to homeostatic scaling both raises concerns and is grounds for optimism. Two important issues warrant investigation. First, our understanding of synaptic adaptations that occur during exposure to HIV neurotoxins, their underlying mechanisms and the time course of their expression is incomplete. Knowing when specific neuronal changes occur during HIV infection is essential to designing effective pharmacotherapy for HAND. Second, if loss of glutamatergic synapses is a mechanism to cope with excess excitation brought on by HIV, it is important to determine whether lost connectivity is a necessary cost for neuronal survival or whether persistent synapse loss is a protective mechanism gone awry. We are optimistic that the increasingly well delineated signaling mechanisms that regulate homeostatic scaling will reveal pharmacological targets suitable for normalizing synaptic function in chronic neuroinflammatory states such as HAND.

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Compliance with Ethical Standards

Conflict of interest The authors declare they have no competing interests.

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