Chapter 5

The Role of Glutathione in Viral Diseases of the Central Nervous System

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Additional information is available at the end of the chapter

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Abstract

The function and physiology of the central nervous system (CNS) can be affected by of bacterial, fungal, protozoan, and viral infections. The neurological effects of viruses are associated with direct infections of structures of the CNS, the migration of infected leukocytes to the CNS, or/and the immune response to control the infection. In all these situations, we have reactive oxygen species (ROS) generation. ROS induces several cellular effects, including cell cycle progression, apoptosis, DNA damage, senescence, and neurodegeneration. The control of ROS involves the glutathione (GSH) balance, owing to antioxidant activity. Moreover, GSH is related with the transport of endogenous/exogenous molecules to extracellular medium by ABCC1/MRP1 activity. The depletion of GSH levels characterizes viral infections and associated-disease progression. Many studies correlated the GSH levels with immune response and suggest adding the glutathione replenishment to highly active antiviral treatment. Thus, it is important to review the relationship between the CNS, immune response, and GSH levels during neurological viral diseases.

Keywords: GSH, JC virus, CMV, HIV-1, HTLV-1, central nervous system, neurological viral diseases, ABCC1/MRP1, immune response

1. Introduction

There are many infectious pathogens that are etiologic agent of central nervous system (CNS) diseases, including the broad categories of bacteria, fungi, parasites, and virus. These infections are an important cause of morbidity and mortality in the world. The viral CNS infections are associated with meningitis and encephalitis development principally. However, the viral infections also are related with diseases in the CNS characterized by the presence of leukocyte

infiltration and inflammation, inducing a progressive damage [1], such as the progressive multifocal leukoencephalopathy with the John Cunningham virus (JC), AIDS-related dementia complex observed in HIV-1-infected patients, neurodevelopmental sequelae (mental retardation, cerebral palsy, and sensorineural hearing loss) caused by congenital cytomegalovirus (CMV) infection or cerebral mass lesions in immunocompromised adults CMV-infected, and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) that affects the human T-cell lymphotropic virus type 1 (HTLV-1)-infected individuals.

In normal oxidative metabolism, the free radical formation is expected. During the 1950s, researchers observed the occurrence of reactive oxygen species (ROS) during molecule irradiation with X-rays and as an effect of normal enzyme metabolic activity. They started to propose that the formation of oxygen free radicals induced tissues and cell damage [2]. At the same time, it was suggested that the mice treatment with glutathione (GSH) inhibited the animal deaths caused by X-ray irradiation [2, 3].

GSH is a tripeptide synthesized in all mammalian cells from the amino acid precursors L-glutamate, L-cysteine, and glycine, through the reactions catalyzed by γ-glutamylcysteine and GSH synthetase. Physiologically, 98% of intracellular glutathione is found in reduced form, and only 2% is detected under oxidized form (GSSH) or joined with other molecules [4]. Glutathione (GSH) has an important role in cellular physiology and metabolism, including antioxidant activity and induction of cellular proliferation [5]. Furthermore, the GSH-dependent antioxidant enzymes (glutathione peroxidase-1, glutathione reductase, glutathione S-transferase) cooperate and are interconnected reactions that eliminate ROS or controlled the redox state. Dysregulation of GSH synthesis was associated with many diseases, such as diabetes mellitus, cholestatic liver disease, endotoxemia, alcoholic liver disease, cancer, and neurodegenerative diseases. During aging the GSH content was decreased in the liver, lung, kidney, red blood cells, spleen lymphocytes, cerebral cortex, and cerebellum. This GSH concentration decline was related with the reduced expression of proteins involved in GSH synthesis. The GSH levels have been studied in Alzheimer's and Parkinson's diseases and others conditions [6]. However, the CNS is exposed to many situations that can induce a cell and tissue damage associated with ROS production. In this chapter, we will discuss some aspects of the balance of GSH levels and oxidative stress during viral infections in the CNS.

2. Intracellular levels of GSH in viral-infected cells and related cellular alterations

The JC virus is a double-stranded (ds) DNA virus from Polyomaviridae family. The mechanism of human-to-human transmission of the JC virus has not been established. It has been suggested that the ingestion of contaminated water and food represents the portal of entrance of this virus in human. The virus entry in the CNS goes through the blood-brain barrier (BBB), infecting the brain microvascular endothelium cells. The virus also infects B lymphocytes in the periphery that like a Trojan horse infiltrated the CNS in immunocompromised patients. There the virus infects oligodendrocytes and astrocytes [7]. JC virus is an etiologic agent of progressive multifocal leukoencephalopathy (PML), a demyelinating disease. Unfortunately, this disease is currently

untreatable and fatal. The relationship between progressive multifocal leukoencephalopathy and GSH still remains unknown. Moreover, JC virus has also been related with CNS tumors, astrocytomas, glioblastomas, neuroblastomas, and medulloblastomas in immunosuppressed and non-immunosuppressed individuals [8]. However, GSH and GSH-related enzymes constitute an important mechanism of drug and multidrug resistance to glioblastomas, as described below [9].

CMV is a member of *beta*-herpesvirus subfamily, in the family Herpesviridae. It is the largest human herpesvirus, with a 230-kb ds DNA genome infection. Virus is spread from infected individual to noninfected individual by body fluids, such as urine, saliva, blood, tears, semen, and breast milk. In addition, a CMV-infected woman can pass the virus to her developing baby during pregnancy [10]. Congenital CMV infection causes serious neurodevelopmental sequelae, including mental retardation, cerebral palsy, and sensorineural hearing loss. CMV also is an increasingly important opportunistic pathogen in immunocompromised patients, inducing cerebral mass lesions. Antiviral therapy of children with symptomatic CNS congenital CMV infection is effective at reducing the risk of long-term disabilities [11].

In muscle cells the CMV infection induces ROS production minutes after entry. This phenomenon is associated to the virus life cycle. The increase in ROS levels activates the transcriptional factor NF-κB, leading transactivation of the viral genes and inducing the transcription of viral proteins [12]. On the other hand, the infection induces increased levels of GSH to control the ROS generation in vitro. This GSH augment is essential to produce the viral progeny. These data suggested that CMV infection coordinates conditions where ROS levels should be controlled and oxidative stress minimized [13]. However, the CMV infection in peripheral blood erythrocytes of pregnant women induces reduced of GSH and GSH peroxidase levels, leading an increase of H_2O_2 levels. These effects were associated with hemolytic anemia in pregnant women [14]. Although the CMV infection has been demonstrated in human brain cells in vitro, such as endothelial cells, astrocytes, neuronal cells, oligodendrocytes, and microglia [11], these studies did not investigate the role of GSH in CMV infection.

HTLV-1 and HIV were classified to the genus *Lentivirus* within the family of Retroviridae, subfamily Orthoretrovirinae. This virus infects leukocytes, which circulate in the blood and lymphatic vessels and may infiltrate in the spinal cord or brain, inducing a neurological diseases [7]. These viruses can be transmitted vertically from mother to child during transplacental transfer, delivery, or breastfeeding, by sexual contact and parenterally through the transfusion of the blood, organ transplant, and blood components or through contaminated needles.

HTLV-1 is the etiological agent of the adult T-cell leukemia/lymphoma and HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a chronic progressive disabling disease characterized by demyelination, axonal loss, neuronal degeneration, and gliosis. The main site of neurodegeneration is the thoracic spinal cord; this leads to a slowly progressive spastic paraparesis with low back pain and bowel, urinary, and sexual dysfunction. The treatment consists in diminishing the symptoms, using corticosteroid therapy [15, 16]. It was demonstrated that Tax, a HTLV-1-viral protein, induces an increase in ROS generation, causing DNA damage and cellular senescence [17]. Moreover, it was observed that the persistence of the virus in infected cells involves mitochondrial ROS production modulated by viral protein p13 [18]. The CD4+ T lymphocytes are the main targets of HTLV-1 infection, but it has been

shown that other leukocytes and glial cells are also infected [19–21]. The infected cells can migrate to the spinal cord and induced the HAM/TSP development. HTLV-1-infected individuals present a spontaneous T-lymphocyte proliferation. This phenomenon is related to the HTLV-1-proviral load and the persistence of the infection. The spontaneous proliferation induced by HTLV-1 infection depends on intracellular GSH levels. Using a GSH synthesis inhibitor, DL-Buthionine-[S,R]-sulfoximine (BSO), the spontaneous proliferation induced by HTLV-1 was impaired in peripheral blood mononuclear cells (PBMC) from infected donors. On the other hand, the GSH precursor induces an increase in mitogen-stimulated cellular proliferation in HTLV-1-infected individuals [19]. Thus, modulation of GSH levels could be proposed as a therapeutic target in HTLV-1-associated diseases.

HIV infection is associated with acquired immune deficiency syndrome (AIDS) development. Combinations of antiretroviral drugs administered as highly active antiretroviral therapy (HAART) reduced the AIDS mortality. However, since 1997 it has been described that 10–20% of virus-infected individuals present HIV-associated dementia [22]. Moreover, the HIV infection also causes mild neurocognitive disorder and demyelinating neuropathy with motor and sensory impairments. The treatment of neurological diseases in HIV-1-infected individuals is established based at the symptoms in association or not with HAART. After virus entry in the CNS, it infects and replicates in microglia that acquire inflammatory phenotype, inducing a neurological damages [7]. Several groups showed a GSH deficiency in the HIV-infected tissues. Initially, the studies demonstrated that low levels of GSH were related to the impairment of T-cell functions. In this work, the authors observed an increase of survival of AIDS patients after the oral treatment with N-acetylcysteine (NAC) administration, a precursor of GSH [22, 23]. In addition, the thiols level analysis in the cerebrospinal fluid (CSF) from HIV-infected patients indicated a significantly reduction in GSH and cysteinyl-glycine levels. Furthermore, the treatment of HIV-infected patients with S-adenosylmethionine, a precursor of homocysteine that is used in GSH synthesis, induced an increase of GSH levels in CSF [24]. Together, these findings suggested the importance of GSH modulation during HIV infection, but the pathway involved to alter the GSH levels remained unknown. The mechanism of neurodegeneration involves the viral protein, gp41. Neurons' death was observed when these cells were incubated in the presence of lentivirus lytic peptide (LLP-1) that expresses the carboxy terminal cytoplasmic domain of gp41 from HIV-1. In addition, the incubation the neuron cell lines with LLP-1 induced a decrease in GSH levels, mitochondrial membrane depolarization, and H_2O_2 production rapidly. The combination of GSH or NAC with LLP-1 prevented the mitochondrial membrane depolarization and cell death [25].

The development of neurological HIV disorders depends on virus entry in the CNS. To access the CNS, HIV virus particles and the infected cells induce the BBB disruption. HIV envelope protein gp120 and the regulatory virus protein, Tat, are involved in BBB breakdown. The incubation of endothelial brain cells with gp120 and Tat reduced the GSH intracellular levels and decreased GSH/GSSG ratio. These proteins also caused an increase in lipid peroxidation, suggesting that gp120 and Tat played an important role in BBB disruption by induction of oxidative cellular stress in endothelial cells [26].

The antioxidant response signals induce the activation of nuclear factor erythroid-derived 2-like-2 (Nrf2). It is a transcription factor that translocates into the nucleus and binds in the

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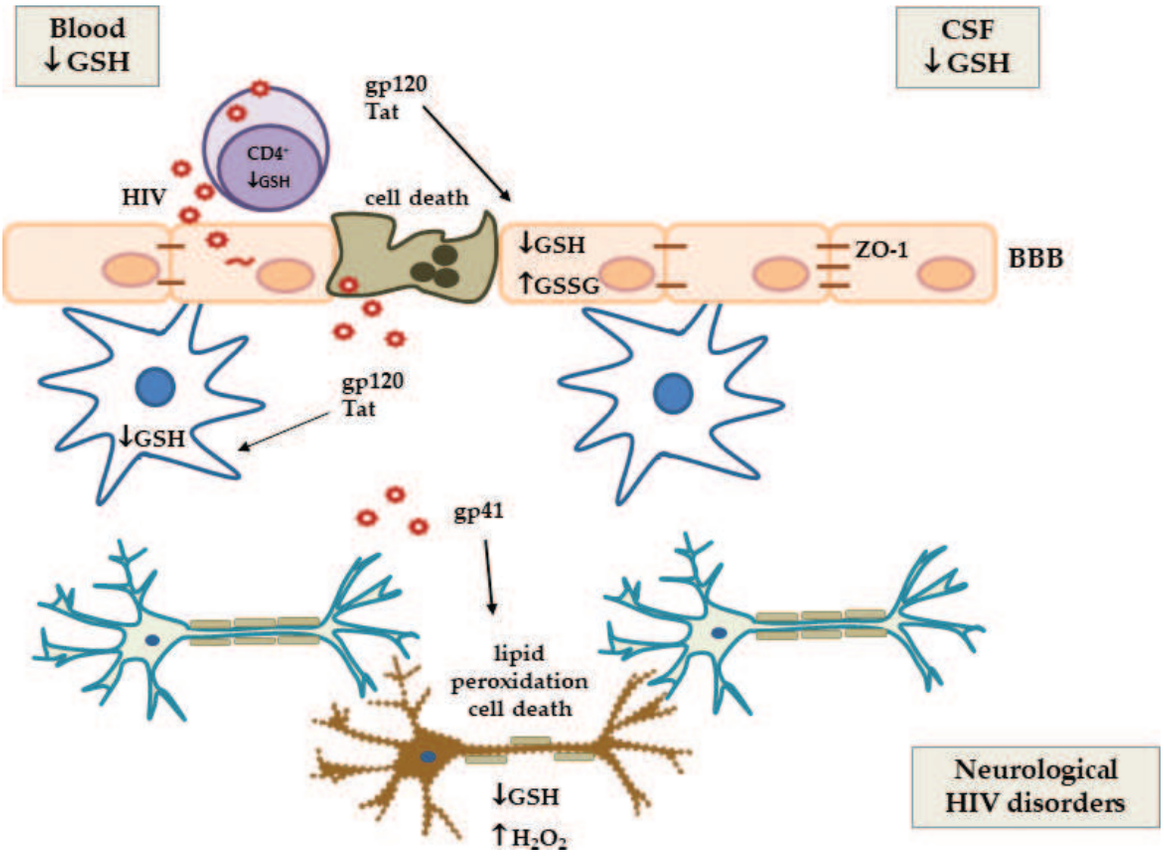

Figure 1. Levels of GSH during HIV-1 infection. In HIV-1-infected patients lower levels of GSH in the peripheral blood and CSF were observed. Alterations in intracellular levels of GSH cells were showed in vivo and in vitro. HIV proteins—gp120, Tat, and gp41—reduced intracellular levels of GSH in endothelial cells, astrocytes, and neurons. The effects of HIV-1-viral proteins also involved BBB breakdown, lipid peroxidation, and cell death.

promoter regions of detoxifying and antioxidants genes [27]. Viral protein Tat enhanced cellular expression of Nrf2 and its translocation into the nucleus. Nrf2 overexpression inhibited the Tat effects, reducing the intracellular ROS and increasing intracellular levels of GSH [28].

The effects of gp120 and Tat can be observed in vivo using a mice model. The administration of gp120 and Tat together or alone decreased GSH and GSH peroxidase brain levels. Animals also presented a reduction of tight junction protein ZO-1, suggesting other effects into BBB, and exhibited augment in lipid peroxidation in the brain [29]. In **Figure 1**, the direct effects of HIV infection in GSH levels and the consequences of this modulation are summarized.

3. HTLV-1 and HIV-1 infection and GSH active transport

GSH is related with the transport of endogenous and exogenous molecules to extracellular medium. GSH is a physiological substrate of ABCC1. Multidrug resistance-related protein 1 (ABCC1) transports several compounds in a GSH-dependent manner; its activity could be stimulated by the GSH intracellular levels. The members of the ABCC family are ATP-dependent efflux pumps, belonging to the ABC family of transport proteins, and they are also

involved in resistance against anticancer drugs. ABCC1 is expressed in tumor cells [30] and normal tissues, such as the brain [31] and lymphocytes [32]. ABCC1 expression depends on Nrf2 activation and translocation to the nucleus [33].

It was already described in this charter; JC virus was detected in CNS tumors, such as glioblastomas. This brain tumor is highly proliferative and invasive and presents mechanisms of multidrug resistance (MDR). It was found that MDR glioblastoma cells displayed lower levels of endogenous ROS and high levels of GSH. On the other hand, the redox state disequilibrium or down modulation of GSH made these MDR cells more sensitive to chemotherapy [9]. In JC virus-infected glioblastoma cells, it is possible to find the same MDR feature. However, the influence of proteins from virus in MDR mechanisms expression remains unknown.

T lymphocytes $CD4^+$ and $CD8^+$ from HAM/TSP asymptomatic and symptomatic individuals presented a reduced ABCC1 expression and activity when compared to uninfected ones [34]. However, a lower ABCC1 expression was detected in CD4+ T lymphocytes from symptomatic patients. This result was directly correlated to the proviral load; a lower expression of ABCC1 was observed in patients with higher proviral load [34]. The pharmacological inhibition of ABCC induced a proliferation increase induced by mitogen of lymphocytes obtained from HTLV-1-infected individuals [19]. The expression and activity of ABCC1 transporter in BBB during HTLV-1 infection still remain unknown. It was suggested that dysregulations of ABC efflux transporters were implicated with the BBB breakdown during neurological diseases [35]. In infectious diseases this phenomenon can be involved in virus entrance in the CNS.

The incubation of astrocytes with gp120 enhanced the mRNA and protein levels of ABCC1. This effect was followed by the increase in substrate fluorescent or GSH transport and decreasing of GSSG efflux. Together these results suggested that the balancing of oxidative cellular status involves the increase in active GSH efflux to extracellular medium [36]. HIV protease inhibitors—ritonavir, indinavir, saquinavir, nelfinavir, and zidovudine—were described as ABCC1 substrate [35], suggesting that the overexpression of ABCC1 in infected cells makes these cells more resistant to chemotherapy.

4. Role of GSH in HIV and HTLV-1 immune response

T $CD4^+$ lymphocyte differentiation involves the antigen-presenting cells (APCs) that display antigen complexed with major histocompatibility complex class II (MHC II) on their surfaces. The antigens are associated to MHC II molecule that interacts with T-cell receptor of T $CD4^+$ lymphocytes, leading the antigen recognition and, subsequently, activation. T-$CD4^+$ lymphocyte activation can generate some profiles (named Th), which depend on molecules present in the microenvironment. The cell phenotype is related with a group of cytokines and other immune products produced by T cell, generating inflammatory or anti-inflammatory cells. During viral infections the activation of inflammatory T-cell phenotype can be associated with virus eradication. However, in the CNS the exacerbation of inflammatory response is related with neurodegeneration [37]. Mice infected with the retroviral complex LP-BM5, a murine model of AIDS, presented GSH and/or cysteine reduction in lymphoid organs (spleen and lymph nodes). This GSH down modulation was followed by change in cytokine profile. The

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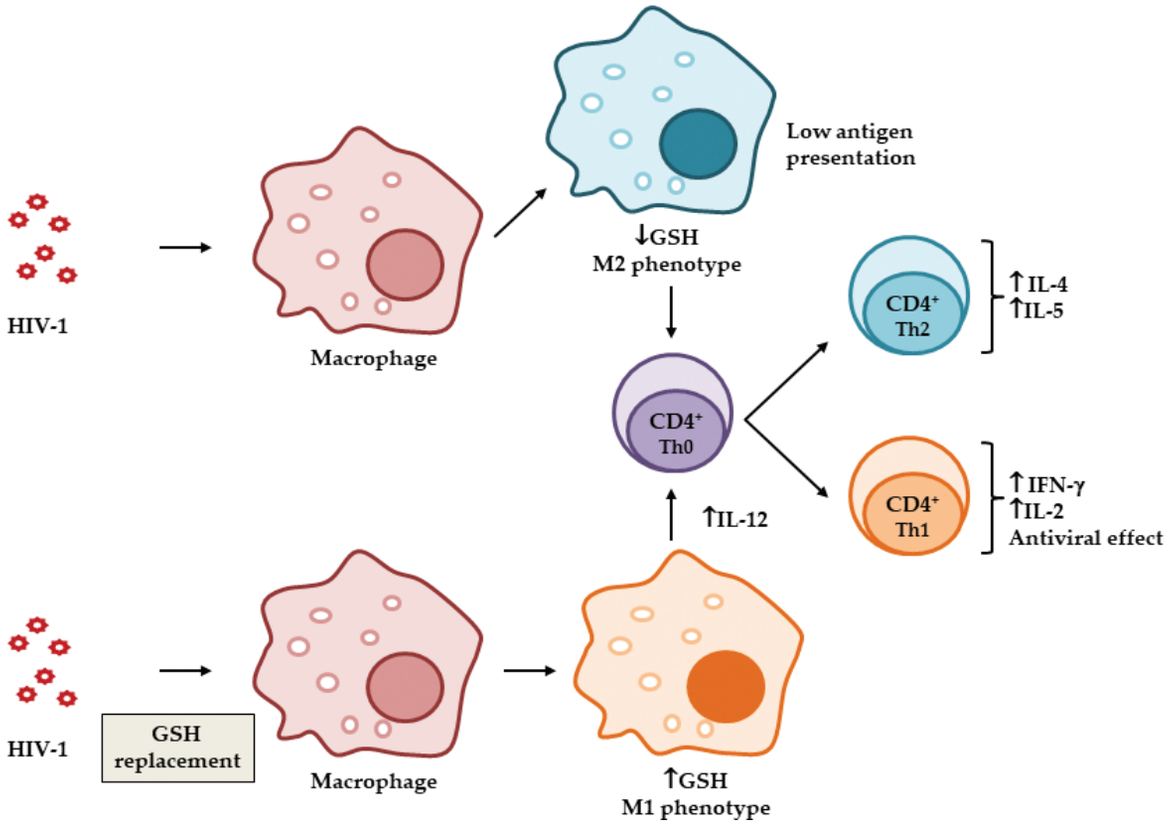

Figure 2. Role of GSH in HIV-1 immune response. The infection induced generation of M2 macrophages and T lymphocytes with Th2 phenotype. However, the GSH replacement led macrophages to M1 differentiation and $CD4^+$ lymphocyte secretion of Th1 cytokines.

infected mice exhibited a higher increase in interleukin (IL) IL-5, IL-4, and IL-2 than IL-12 and interferon-γ (IFN-γ), suggesting an important alteration in cytokine profile from Th1 to Th2 (**Figure 2**) [38].

Macrophages and dendritic cells are an important group of APCs. During infections macrophages can acquire specialized functional phenotypes. Macrophages classic activated are involved in inflammatory responses and are denominated M1. Macrophages alternative activated exhibit an antagonic inflammatory profile and named M2 [37]. Macrophages HIV-1 and LP-BM5 infected exhibited a decrease in GSH and cysteine intracellular levels. In addition, low intracellular levels of GSH were correlated with defective processing of antigens in APCs, indicating that GSH may be a critical factor in antigen processing [39]. During the LP-BM5 infection, macrophage polarization into alternative profile was observed, suggesting that M2 cells were driving the T-cell phenotype. LP-BM5-infected mice treatment with GSH replacement changed the macrophage polarization to M1 profile, inducing an increase in Th1 cytokine production and augmented antiviral response [38]. Thus, GSH modulation causes immune response phenotype alteration, leading to an important impact in virus elimination (**Figure 2**).

T lymphocyte $CD8^+$ is a cytotoxic T cell. They recognize the antigens through binding between TCR and MHC class I associated with antigen peptide. The control of viral infection is directly linked with efficiency of $CD8^+$ cytotoxic response [37]. The treatment with NAC induced an increase in surface activation molecule CD69 expression on unstimulated $CD8^+$ T lymphocytes

obtained from HTLV-1-infected individuals. This result suggested that the increase in CD69 expression on $CD8^+$ lymphocytes from HTLV-1 infected donors was correlated with an augmentation of GSH. Thus, increases in GSH levels could be beneficial to the activation of HTLV-1-specific $CD8^+$ T cell and to the elimination of HTLV-1-infected cells [19].

The neurodegeneration is associated with decontrolled inflammatory responses into the CNS. Inflammatory cytokines induce nitric oxide (NO) and ROS production for innate immune cells and microglial cells. The incubation of microglia cells in the presence of viral protein gp120 was observed to increase in ROS production [36]. Besides, gp120 induces secretion of tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein-1 (MCP-1), leading to neuronal cell death, subsequently [40]. The inflammatory microenvironment reduces the glutamate uptake, inducing accumulation of this excitatory amino acid and excitotoxic neurodegeneration. Although, any study has not related the viral infection, GSH intracellular levels, and excitotoxic neurodegeneration, the literature suggested that antioxidant responses can prevent the neuron death directly or indirectly.

5. Effects of antiviral therapy in GSH levels in the CNS

The strategy used to treat children with symptomatic CNS congenital CMV infection and immunosuppressed individuals CMV-infected is based on doses of ganciclovir. This is an acyclic deoxyguanosine nucleoside analogue [41]. In vivo *s*tudies using mice model infected with CMV demonstrated that the treatment with ganciclovir reduced a viral load and TNFα levels. Moreover, the results suggested that antiviral therapy suppressed the oxidative damage by downregulation of malondialdehyde and upregulation of GSH levels in mice serum [42]. Unfortunately, the role of ganciclovir in CNS oxidative damage related with CMV infection remains unknown.

No antiviral treatment intervention exists for HTLV-1 infection. The HAM/TSP treatment is limited to symptomatic therapy. Usually, symptomatic patients are treated with corticosteroid pulse therapy. During last decades the antiviral therapy against HIV was improved, resulting in a significant reduction AIDS-related mortality and increasing HIV-infected patient survival. The *h*ighly *a*ctive *a*ntiretroviral *t*herapy (HAART) is started with the combination of two nucleoside analogue transcriptase reverse inhibitors and one non-analogue nucleoside transcriptase reverse inhibitor or protease inhibitor plus ritonavir-boosted. The analysis of T $CD4^+$ lymphocytes obtained from the peripheral blood of HIV-1-infected patients showed an increase in GSH levels and decrease in GSSG levels during HAART at 1 year. In this study the patients received one protease inhibitor (indinavir or ritonavir) in combination with two nucleoside analogs (lamivudine plus zidovudine or plus stavudine), suggesting that the HAART ameliorates the oxidative alterations related with HIV-1 infection [43]. However, the effects of HAART on GSH levels may be different in other cell types. Human aortic endothelial cells pre-exposed to HAART produced higher levels of ROS than untreated cells after phorbol myristate acetate stimulation. After the HAART treatment, T-lymphocyte cell adhesion on human aortic endothelial cell monolayer increases significantly. However, the addition of NAC or GSH induced the inhibition of these effects, suggesting that the modulation of antioxidant levels activated the endothelium [44].

The first approved antiretroviral drug was zidovudine (AZT), a nucleoside reverse transcriptase inhibitor. The relationship between AZT and GSH has been studied since 1998. Mice treatment with AZT did not exhibit a significant decrease in GSH in total muscle homogenate, but the GSSG concentration increases, leading an increase in GSSG/GSH ratio. Furthermore, AZT treatment induces a skeletal muscle mitochondrial peroxide production [45]. Similar results were observed in monocytic cell lines incubated in the presence of AZT. The AZT treatment induced a significant reduction in GSH levels and destruction of mitochondria [46]. AZT is the antiretroviral drug with the best intracerebral penetration, however this substance virus resistance mutations in periphery and CNS [47]. The effects of AZT in GSH levels in the CNS have been remained unknown. Zang et al. demonstrated that mouse neuron exposure for short term to AZT did not present alteration in mitochondrial DNA levels. However, the results suggested that AZT long-term exposure caused deletion of mitochondrial DNA and neuron death [48]. Furthermore, AZT or the combination AZT plus indinavir (protease inhibitor) induces oxidative stress in human brain microvascular endothelial cells. These cells represent an important model to study BBB. The combination AZT plus indinavir induced an increase in ROS production, disruption in membrane mitochondrial potential, reduction in intracellular GSH levels, augment permeability of endothelial layer, leading cell death [49]. Together these results suggested that this antiretroviral therapy compromises the BBB and could be associated with HIV-1 neurological diseases.

These findings suggested that the replacement of GSH, reducing the oxidative stress in HIV-1-infected patients, is an interesting therapeutic approach. In some therapeutic strategies, to restore the GSH levels NAC or pro-GSH molecules in combination with HAART have been used. Moreover, the higher levels of GSH improve the antiviral immune response, collaborating in viral load reduction and in maintaining normal T-CD4$^+$ lymphocyte count [50].

6. Discussion and conclusion

In this chapter we explore some aspects about neurodegenerative diseases associated with viral infection, GSH, and oxidative stress. Worldwide, many individuals are afflicted by JC, CMV, HTLV-1, and HIV-1 and develop some neurological diseases. However, studies that describe how the oxidative stress is involved in disease development remain insufficient. The oxidative stress in the CNS is associated to many neurodegenerative diseases. ROS, including reactive nitrogen species, are important mediator of brain and spinal cord damage. They are related with inflammation and mitochondrial and proteasomal dysfunction. The vulnerability of the CNS is associated with the higher consumption of oxygen than other tissues. Oxygen is important in ATP generation process, which is responsible for energy support used during normal CNS function. Physiological ROS levels are essential to neuronal functions, such as enhancing synaptic plasticity, long-term potentiation, and memory formation. However, the brain endogenous antioxidant defenses have not been enough to your demand. Moreover, the complexity of the cell composition of this tissue and the elevated oxygen levels corroborate to elevated capacity of the CNS in ROS production. All cellular macromolecules are susceptible to oxidative harm. ROS level elevation activates the detoxification and repair pathways.

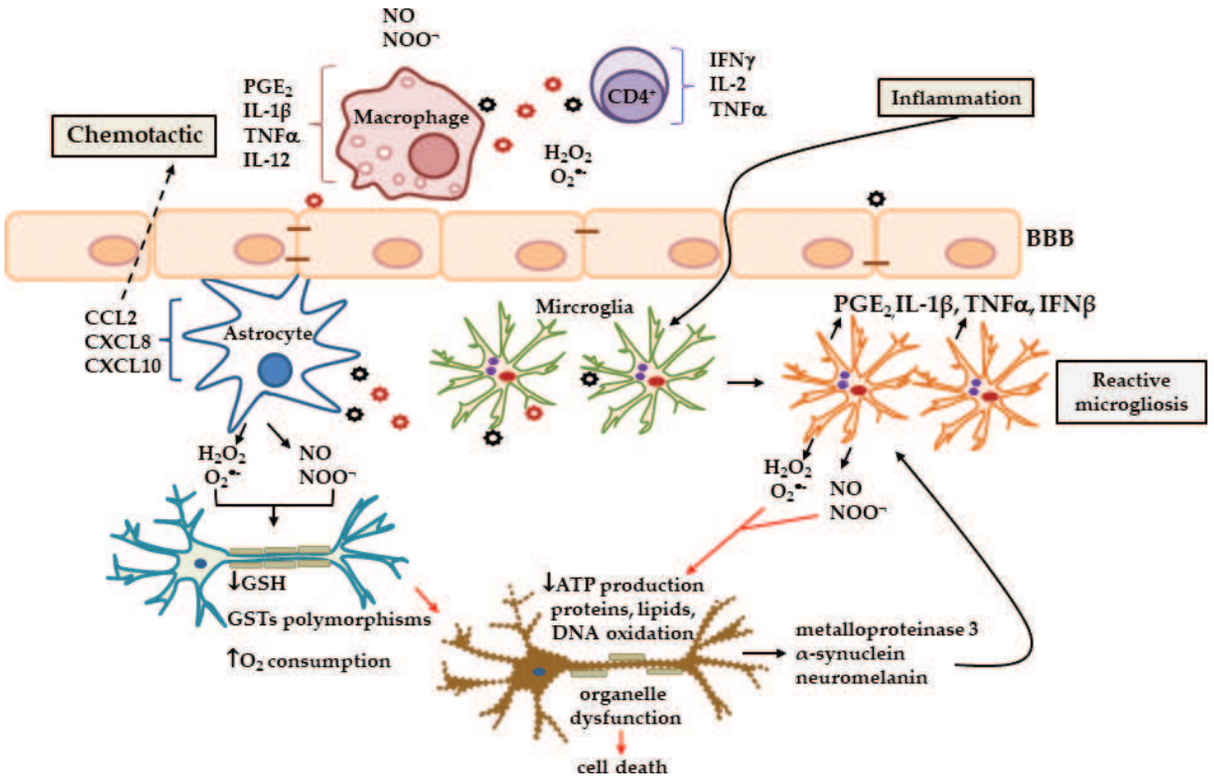

Figure 3. The imbalance of pro-oxidants induces oxidative stress and cell damage. The vulnerability of the CNS: ↓GSH and ↑O_2 consumption. Inflammation triggers microglia. Activated microglia releases inflammatory cytokines, ROS, and RNS. Microglia and astrocytes can be activated via pattern recognition receptors. During astrocyte activation, these cells released ROS, RNS, and chemokines. In this microenvironment neurons presented macromolecule oxidation, mitochondrial disruption, and, consequently, cell death.

The failure in these processes produces oxidation of proteins; lipids and DNA; consequently, organelle dysfunction; and after that neuronal damage. The critical organelle affected is the mitochondria, whose disruption induces reduction in ATP generation and apoptosis or necrosis [51]. As previously described the viral infection induced an increase in ROS production directly in CNS cells or indirectly by the infiltrated activated immune system cells, which use ROS release as mechanism to control the infection (**Figure 3**).

Glial cells (astrocytes and microglia) play important roles in maintaining CNS homeostasis through some processes, including reduction of oxidative stress. During neurodegenerative disorder glial cells release some factors to reestablish integrity and repair damaged cells. However, during the chronic inflammation, the glial activation causes an increase of ROS production and other neurotoxic mediators, leading a neuronal damage [52]. The principal cell type involved in CNS inflammation is the microglia. Microglia expresses some pattern recognition receptors that are engaged by pathogen-associated molecular patterns, triggering microglia activation. Activated microglia produced inflammatory mediators, such as prostaglandin E_2, interleukin-1β TNFα, ROS (peroxide—H_2O_2, superoxide—$O_2^{\bullet-}$), and reactive species nitrogenous (RNS: NO; NOO- peroxynitrite). This phenomenon induces neuron damage. Damaged dopaminergic neurons release matrix metalloproteinase 3, α-synuclein, and neuromelanin that superactivated microglia, inducing reactive microgliosis, enhancing of the neurotoxicity-related mediators, such ROS (**Figure 3**). Moreover, ROS exerts an important effect on microglia as the

second messenger, modifying inflammatory gene transcription and, consequently, amplifying the inflammation. During reactive microgliosis an increase of GSSG levels is observed. Studies in Parkinson have been suggested that dopaminergic neurons from substance nigra can be associated to GSH deficiency, becoming these cells more vulnerable to ROS [53].

The glutathione transferase (GST) activity can be relate to sensibility of neurons of ROS. GSTs conjugate molecules, including xenobiotics, with GSH, and then, this conjugated molecules can be actively transported to extracellular medium by ABCC transporters. Moreover, GSTs are involved in c-Jun N-terminal kinase (JNK) signaling pathway. ROS causes GSTs-JNK-c-Jun complex formation blocking JNK signaling pathway and preventing the events associated with this signaling cascade. GST gene polymorphisms have been identified and produce an important impact in enzyme activity. Some studies demonstrated that GST gene polymorphism carries have a positive correlation with brain cancer, Alzheimer's disease, and Parkinson's disease development risk [54]. The positive correlation between GST gene polymorphisms and hepatocellular carcinoma caused by hepatitis B virus chronic infection [55] and uterine cancer associated to human papilloma virus infection was described [56] (**Figure 3**). However, the relationship between GST gene polymorphisms and viral diseases of the CNS remains unknown.

The major studies relating viral infection and glia cells have been developed in HIV-1 model infection. Microglial cells exposed to HIV viral protein Nef release IFNβ. Then, IFNβ induces iNOS expression and NO production [57]. Furthermore, HIV-1 protein Tat induces NADPH oxidase activity in astrocytes. ROS produced by NADPH oxidase activity was related to chemokine (CCL2, CXCL8, and CXCL10) production, and it was inhibited by the treatment of astrocytes with NAC or NADPH oxidase inhibitors [58]. Together these results suggested that the HIV infection induces glia cell activation, ROS, and RNS which are directly involved in production of inflammatory mediators. The imbalance of prooxidants induces oxidative stress and cell damage (**Figure 3**).

The studies in viral diseases of the CNS have suggested an important link between GSH, immune response, and antiviral response. The findings indicated that the GSH replenishment can be used in highly active antiviral treatment. However, in asymptomatic HTLV-1 carries, this clinical approach should be the opposite result. The importance to study the relationship between GSH levels and viral neurological diseases is clear.

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Conflict of interest

The authors declare no conflict of interests.

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