INTRODUCTION

Neurological disorders represent a prominent feature of the human immunodeficiency virus type 1 (HIV-1) infection, usually occurring during the last stages of acquired immunodeficiency syndrome (AIDS) [1]. Neurological problems appear in this case even in the absence of opportunistic infection or secondary cancer. Approximately one-third of adults and half of children with AIDS eventually have neurological complications. The most common disorder in HIV-1-infected individuals is encephalopathy, a fatal illness causing severe dementia. Events leading to encephalopathy are unclear, but infiltration by monocytes and macrophages is a consistent finding in the central nervous system (CNS) of AIDS patients [2]. The neurological symptoms consist of motor, sensory, and cognitive disorders, commonly termed HIV-1-associated cognitive/motor complex (AIDS dementia complex) [3, 4]. A severe form of this impairment occurs in 20-30% of immunosuppressed patients with neurological deficits. Virus-induced brain pathology includes neuronal loss, astrocytosis, and myelin pallor [1]. Despite HIV-1 not directly infecting neurons, there is profound neuronal loss in the cortex and retina [5-8].

HIV-1 predominantly infects the cells that express the CD4 receptor, which serves as the major receptor for HIV-1, utilizing the CD4 molecule for entry into T cells and macrophages [9, 10]. Monocytes/macrophages function as a cellular reservoir for HIV-1, since macrophages can be infected with the virus, but are resistant to its cytopathic effects. The ability of HIV-1 to establish a latent infection in macrophages may contribute to the spread and persistence of the virus. A number of cellular factors can modulate replication of latent virus. In particular, proinflammatory cytokines have been shown to up-regulate the expression of HIV-1 [11, 12]. HIV-1 penetration to the brain is a pivotal event in the neuropathogenesis of AIDS-associated dementia. Gendelman et al. [13] suggested that HIV-1-infected monocytes have an advantage in binding to microvascular endothelial cells, and that this binding facilitates entry of the virus into brain tissue. Morphometric techniques have given new insights into the damage observed in AIDS-impaired brains [8, 14]. Although no atrophic changes were seen at the macroscopic level, a significant loss of neurons was found in the frontal, parietal, and temporal cortices [5, 8, 14]. The pathogenesis of AIDS dementia complex has remained elusive, as HIV-1 infection has been detected in macrophages and microglia but not in neurons [15, 16]. Takahashi et al. [17] demonstrated that latent or low-level infection of astrocytes occurs in AIDS, a finding that may be of importance for understanding neuropathogenesis. The infection of astrocytes is highly
unusual and may occur in children [18-20]. There is good evidence that there are two stages in the infection of brain macrophages by HIV-1. Initially, the viral coat glycoprotein gp120 binds to a receptor CD4 on the surface of macrophages, but other binding sites may also exist. Internalization of the virus may stimulate macrophages to release low levels of neurotoxins. HIV-1 proteins, such as gp120 and possibly Tat and Nef, can stimulate uninfected cells to release similar neurotoxins [20]. In the second stage of HIV-1 infection, the viral genome is integrated into the genome of macrophages, and active virus replication ensues. During this stage, macrophages release large amounts of neurotoxic substances. The toxins produced by macrophages include glutamate-like neurotoxic molecules, free radicals, cysteine, platelet-activating factor (PAF), cytokines, eicosanoids, such as arachidonic acid, and also unidentified factors emanating from stimulated macrophages and/or reactive astrocytes [16, 20-23]. Interactions among several different types of cells, including mononuclear phagocytes, astrocytes, and neurons, probably regulate the secretion of neurotoxins by HIV-1-infected macrophages [20].

MACROPHAGES AS MEDIATORS OF HIV-1-ASSOCIATED NEUROTOXICITY

The role that microglia play in HIV-1 infection is important for understanding the pathogenesis of HIV-1 infection and the resulting brain damage. Most of the current evidence strongly suggest that microglial cells arise from mesodermal tissues, ultimately develop from bone marrow cells, in particular monocytes [24], and populate the CNS after it has been vascularized. Microglia are generally considered to include bone marrow-derived resident macrophages in the brain and thus form the interface between the CNS and the immune system. Microglia constitute ~10% of the total glial cell population. These cells can be considered a specialized subtype of tissue macrophages found in the CNS [25, 26]. The major known function of microglia is as scavenger cells. Also, microglia may be involved in inflammation and reparative processes in the CNS because of their phagocytic ability, release of neutral proteinases, and production of oxidative radicals. Microglia have been demonstrated to express major histocompatibility complex antigens (class-I and class-II MHC) upon activation, act as antigen-presenting cells, release a number of immunoregulatory cytokines, and respond to cytokine stimulation, suggesting an involvement with inflammatory and immune responses within the CNS [26]. Microglia may play an important role in a variety of neurological disorders such as AIDS dementia complex, Alzheimer’s disease, and amyotrophic lateral sclerosis [27]. Although microglia resemble tissue macrophages in immunological phenotype and function, there are some differences between microglia and other monocyte/macrophage lineage, which still remain to be clarified [28]. Microglial cells, the target cells for HIV-1 in the brain, are responsible for the replication and spread of the virus. They fuse together to form the multinuclear giant cells, which are considered to represent the hallmark of HIV-1 infection. A combination of immunohistochemistry and morphometry to investigate the activation pattern of microglia gave conclusive data. The number of activated microglial cells was significantly increased in the HIV-1-infected brains. The activation of microglia did not correlate with the presence of HIV-1 antigen in brain tissue [14].

One factor that may contribute, at least in part, to AIDS dementia complex is neuronal injury caused by the viral envelope protein, gp120, or a fragment thereof, which can be shed from HIV-1 harbored by macrophages or microglia in the CNS [29-32]. It was found that picomolar concentrations of gp120 appeared to be toxic in vitro to rodent neurons [29]. The HIV-1 coat protein gp120 produces lesions in cultured neurons and glial cells. This envelope protein produces neuronal cell damage in primary cultures of a variety of cell types, including hippocampal and retinal ganglion cell neurons [29]. The importance of macrophages as mediators of gp120-associated neurotoxicity is shown by the failure of gp120 to cause neuronal damage after macrophages had been eliminated from retinal ganglion cell cultures [15]. The properties of primary cell cultures, however, are often markedly different from those of cells living in their normal environment. The use of an in vitro organized structure will enable the molecular and cellular mechanism of action of gp120 to be examined under conditions particularly suitable and relevant to the in vivo situation [33]. The protein gp120 induces widespread chromatin condensation and lesions in pyramidal granular neurons and in interneurons of rat hippocampal organotypic slice cultures. This damage is clearly of an apoptotic (programmed cell death) type [33]. In a study using transgenic mice, Toggas et al. [34] demonstrated that damage to the CNS can be caused by the HIV-1 coat protein gp120. This mouse model has its shortcoming. Transgene for gp120 is expressed in astrocytes rather than in the macrophage/microglial lineage, the cell type predominantly infected in the CNS [16].

Neuronal cell death elicited by gp120 is absolutely dependent on the presence of glutamate, acting through N-methyl-D-aspartate (NMDA) receptors [31, 35, 36], and is mediated by excitotoxic mechanisms. These studies were extended by evidence that gp120 could indirectly trigger a dramatic and potentially lethal rise in neuronal [Ca²⁺], by releasing toxic factors from activated macrophages/microglia and, possibly, astrocytes [15, 30]. Recently, human macrophages and