ISSN 0233-7657. Биополимеры и клетка. 1997. Т. 13. № 4

Mechanisms of HIV-1 mediated neurodegeneration promoted by macrophages and astroglial factors

I. S. Magura, O. M. Rozhmanova

Bogomolets Institute of Physiology, National Academy of Sciences of Ukraine
252024, Kiev, Bogomolets str., 4

Neurological disease is a prominent feature of human immunodeficiency virus type 1 (HIV-1) infection, usually occurring during the last stages of acquired immunodeficiency syndrome (AIDS). The neurologic cognitive impairment, termed HIV-1-associated cognitive/motor complex (AIDS dementia complex). Astrocytes and microglia are key participants in mediating the neurologic dysfunction associated with HIV infection of the central nervous systems. The neuropathogenesis of HIV-1 infection is related to secretory neurotoxins from activated HIV-1-infected macrophages The toxins produced by the macrophages include glutamate-like neurotoxic molecules, free radicals, cysteine, platelet-activating factor, cytokines, and eicosanoids such as arachidonic acid, and as yet unidentified factors emanating from stimulated macrophages and/or reactive astrocytes.

The rate of progression to disease varies considerably among individuals infected with HIV-1. Most individuals infected with HIV-1 remains disease free for many years and during this time, maintain relatively stable numbers of $CD4^+$ T cells, strong cytotoxic T cell responses, and low numbers of HIV-1-infected cells in the blood, all indicators that the virus is under immune control. At some point the immune system falters, and most infected individuals progress to develop the symptoms of AIDS [1].

HIV-1 predominantly infects 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 [2, 3]. CD4 by itself was not sufficient for HIV-1 infectivity; some «cofactor», only found in human cells, was also required [4]. Berg at al. [5] report the discovery of a membrane protein they call «fusin», which has the expected characteristics of the elusive HIV-1 cofactor. This protein is a putative G protein-coupled receptor with seven transmembrane segments. The researchers found, that together with CD4, it permits cells to fuse with HIV-1 surface — a key step in the infection process. Recent evidence suggests that chemokines and their receptors may play an important regulatory role in HIV-1 infection [6—8]. Chemokines are chemotactic cytokines that acvtivate and direct the migration of leukocytes.

Monocytes/macrophages functione as a cellular reservoir for HIV-1 since macrophages can be infected with the virus but are resistant to its cytopathic effects [9, 10]. The ability of HIV-1 to establish a latent infection in macrophages may contribute to the spread and persistence of the virus [11]. HIV-1-infected monocytes express higher levels of cell surface adhesion molecules, such as the β_2 integrins, and secrete larger amounts of proteolytic enzymes, such as metalloproteinase-9 [12]. These changes in monocyte function could participate in the pathogenesis of AIDS by promoting tissue invasion and by enhancing local tissue proteolysis [13]. Lafrenie et al. [14] shown that many of the effects of HIV-1 infection of monocytes can be mimicked by treatment of the monocytes with a regulatory gene product of the HIV genome HIV-1-*Tat*. Monocytes treated with soluble HIV-1-*Tat* protein express elevated levels of β_2 integrins, which mediates monocyte aggregation and monocyte adhesion to endothelial monolayers, and increases monocyte production of matrix metalloproteinase-9. The changes in monocyte function are similar to those seen either in response to cytokine treatment or during an inflammatory response when monocytes are induced to extravasate. Lafrenie et al. [14] presented evidence that HIV-1-*Tat* protein can

enhance the chemotactic and invasive behaviors of monocytes and could play an active role in the recruitment of monocytes into extravascular tissues in addition to activating circulating monocytes. A number of cellular factors can modulate replication of latent virus. In particular, proinflammatory cytokines have been shown to up-regulate expression of HIV-1 [15, 16]. Macrophages are the major source of virus in tissues such as brain, and spinal cord. Neurological disease is a prominent feature of HIV-1 infection, usually occurring during the last stages of AIDS [17]. Neurologic problems occur even in the absence of opportunistic infection or secondary cancer [18—20]. Approximately one third of adults and half of children with the AIDS eventually have neurologic 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 [11].

The neurologic signs consist of motor, sensory, and cognitive impairment, termed HIV-1-associated cognitive/motor complex (AIDS dementia complex) [21, 22]. A severe form of this impairment, occurs in 20—30 % of immunosuppressed patients with neurological deficits. Virus-induced brain pathology is characterized by productive infection of cells of monocytic/macrophage lineage [23, 24] in the CNS accompanied by diffuse and nodular microgliosis, multinucleated giant cell formation, astrocytosis, and myelin pallor [19, 20, 25, 26]. Despite HIV-1 not directly infecting neurons, there is progressive loss of specific neuronal population in the neocortex [27—30], limbic system, and basal ganglia in association with synaptic and dendritic damage, neuronal loss in retina [30—33].

Macrophages as mediators of HIV-1-associated neurotoxicity. HIV-1 penetration of the brain is a pivotal event in the neuropathogenesis of AIDS-associated dementia. The recruitment of mononuclear phagocytes into brain during disease likely governs the tempo and progression of CNS disease. Nottet et al. [34] suggest that HIV-1-infected monocytes have an advantage in binding to microvascular endothelial cells and that this binding facilitates entry of virus into brain tissue. HIV-1-infected monocytes would induce the expression of adhesion molecules on brain microvascular endothelial cells that allow binding and then penetration of virus-infected monocytes into brain. Since immune-activated HIV-1-infected macrophages overexpress proinflammatory cytokines, such as TNF-α, activated cells might have a selective advantage in transendothelial migration [34]. 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 the macrophage, but other binding sites may exist. Internalization of the virus may stimulate the macrophage 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 [35]. In the second stage of HIV-1 infection, the viral genome is integrated into the genome of the macrophage, and active virus replication ensues. During this stage macrophages release large amounts of neurotoxic substances. The toxins produced by the macrophages include glutamate-like neurotoxic molecules, free radicals, cysteine, platelet-activating factor (PAF), cytokines, and eicosanoids, and as yet unidentified factors emanating from stimulated macrophages and/or reactive astrocytes [35—39]. Interactions among several different types of cell, including mononuclear phagocytes, astrocytes, and neurons, probably regulate the secretion of neurotoxins by HIV-1-infected macrophages [35].

Takahashi et al. [40] demonstrated that latent or low-level infection of astrocytes occurs in AIDS, a finding that may be of importance in understanding neuropathogenesis. The infection of astrocytes is highly unusual and may occur in children [35, 41, 42].

The role that microglia play in HIV-1 infection is important in the understanding of the pathogenesis of HIV-1 infection and of the resulting brain damage. Most of the current evidence strongly suggest that microglia arise from mesodermal tissues, ultimately develop from bone marrow cells, in particular the monocyte [43], and populate the CNS after it has been vascularized. Microglia are generally considered to be bone marrow-derived resident macrophages in the brain and thus form the interface between CNS and immune system. Microglia constitute $\approx$ 10 % of the total glial cell population. They can be considered as a specialized subtype of tissue macrophage found in the CNS [44, 45]. The major known function of microglia is as a scavenger cell. Also, microglia may be involved with inflammation and repair 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 (MHC class I and II) upon activation, act as antigen-presenting cells, secrete a number of immunoregulatory cytokines, and respond to cytokine stimulation, suggesting an involvement with inflammatory and immune responses within the CNS [45]. Microglia may play an important role in a variety of neurological disorders such as AIDS, Alzheimer's disease, and amyotrophic lateral sclerosis [46]. Although microglia resemble tissue macrophage in immunological phenotype and function, there are some differences between microglia and other monocyte/ macrophage lineage that still remain to be clarified [47]. 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 be the hallmark of HIV-1 infection. The combination of immunohistochemistry and morphometry to investigate the activation pattern of microglia gave conclusive data. The number of activated microglia was significantly increased in HIV-1 infected brains. The activation of microglia was not correlated with the presence of HIV-1 antigen in brain tissue [48].

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 harboured by macrophages or microglia in the CNS [49—53]. It was found that picomolar concentrations of *gp120* were toxic *in vitro* to rodent neurons [49]. The HIV-1 coat protein *gp120* produces lesions in cultured neurones and glial cells. The HIV-1 envelope protein *gp120* produces neuronal cell damage in primary cultures of variety of cell types including hippocampal neurons and retinal ganglion cell [49]. The importance of macrophages as mediators of *gp120*-associated neurotoxicity is shown by the failure of *gp120* to cause neuronal damage when macrophages were eliminated from retinal ganglion cell cultures [54].

The properties of primary cell cultures are, however, 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 in conditions which are particularly suitable and relevant to the *in vivo* situation [55]. *Gp120* induces widespread chromatin condensation and lesions in pyramidal granular neurone and in interneurones of rat hippocampal organotypic slice cultures. This damage is clearly of an apoptotic (programmed cell death) type [55]. In an study involving transgenic mice Toggas et al. [56] demonstrate that damage in 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 [57].

Neuronal cell death elicited by *gp120* is absolutely dependent upon the presence of glutamate acting through N-methyl-D-aspartate (NMDA) receptors [51, 58, 59] and to be mediated by excitotoxic mechanisms. These works were extended by evidence that *gp120* could indirectly trigger a dramatic and potentially lethal rise in neuronal $[Ca^{2+}]_i$ by releasing toxic factors from activated macrophages/microglia and possibly astrocytes [54, 50]. The NMDA receptors has received substantial attention because of its high Ca^{2+} permeability and its involvement in synaptic plasticity, long-term potentiation, learning and memory, and neurodegeneration [51, 60, 61]. Activation of NMDA receptors leads to increased intracellular Ca^{2+} followed by activation of protein kinases, phospholipases, proteases, nitric oxide synthase (NOS), impaired mitochondrial function, and the generation of free radicals [59, 62—64]. Neurotoxicity in primary neuronal cultures induced by stimulation of NMDA receptors is mediated in part by nitric oxide (NO) [59, 65]. NO is a powerful endogenous mediator for numerous physiological responses, as well as in manifestations of brain injury [66, 67]. Bukrinsky et al. [68] demonstrated that HIV-1 infection of human monocytes results in the appearance of inducible isoform of NOS. Human monocytes have been used as model of brain macrophage function. The appearance of the inducible isoform of NOS is accompanied by significant production of NO. This NOS induction is subject to both positive and negative regulation by the immune system cytokine network. NO-mediated neurotoxicity is engendered by reaction with O_2^-, apparently leading to formation of peroxynitrite ($ONOO^-$), a highly destructive radical. The formation of a $ONOO^-$ leads to lipid peroxidation and indiscriminate oxidation of sulphhydryls and kills neurons in a dose-dependent fashion [65]. In other oxidation states NO can interact with thiol groups of NMDA receptors and ameliorate deleterious effect of glutamate [65, 69]. Recently, human macrophages and astrocytes have been shown to produce NO via inducible NO synthase (iNOS) in response to cytokines and *gp120* [59, 70, 71]. Although *gp120* can bind to CD4 on human macrophages it has been argued that this is not true for rodents. Thus, the effects of *gp120* in the rodent nervous system might imply the existence of another, as yet unknown, receptor for the coat protein. Other HIV proteins, such as *Tat* and *Nef*, were shown to be toxic in the rodent CNS, raising questions about the specificity of the findings with *gp120* [54].

Evidence has been accumulating that brain damage in HIV infection is not the result of a direct effect of the virus. The neuronal damage is, rather, due to toxic factors that alter the neuronal function. The discrepancy between widespread neuronal damage and the absence of productive viral infection in neurons led to the hypothesis that HIV-1 induces neurotoxicity through an indirect mechanism [35]. Recently, a new human neuronal culture system, called NT neurons, has become available [72]. A new *in vitro* system comprising a pure population of neurons, human NT cells, was used to characterize the direct neurotoxic effect of HIV-1 envelope protein *gp120*. Treatment of mature NT neurons with various doses of *gp120* for 24 h caused a decrease of up to 27 % in the number of viable cells. These data indicate the possibility that *gp120* exerts a direct

neurotoxic effect by acting through NMDA receptors and Ca^{2+} channels [73].

Macrophages and microglial cells produce prostaglandin E_2, cytokines such as tumor necrosis factor (TNF-α), transforming growth factor-β (TGF-β), interleukin-1 (IL-1), interleukin-6 (IL-6), colony stimulating factors (CSFs). Many cytokines cause death of oligodendrocytes and/or destruction of myelin *in vitro* [74, 75]. These potent, cell-derived effector molecules are cytotoxic when added to primary neuronal cultures and are also detected in the cerebrospinal fluid of HIV-infected subjects with neurological deficits [76, 77]. Increased levels of TNF-α, IL-1-β are present in the brains of patients with various pathological conditions such as AIDS [78], multiple sclerosis [79], Alzheimer's disease, and Down's syndrome [80]. Numerous studies have demonstrated that inflammatory cytokines are present in CNS during neurological diseases. These cytokines include IL-1, IL-6, INF-γ, TNF-α and TNF-β. Interferon-γ (INF-γ), which are neurotoxic, is involved in the pathogenesis of neuronal injury in patients with HIV-1 infection [76, 77]. INF-γ is the product of activated T cells and has a wide range of immunoregulatory functions. INF-γ would be present in the CNS only during disease states where the blood-brain barrier has been breached [77]. It was demonstrated that interactions between HIV-infected monocytes and astroglial cells produce high levels of proinflammatory cytokines (TNF-α, IL--1β), PAF [81], and eicosanoids [82]. Several cytokines can regulate their own synthesis, as well as the production of other cytokines (for example, IL-1, TNF-α).The most abundant source of cytokines appears to be activated microglia, although neurones, astroglia, perivascular and endothelial cells can also express cytokines.These molecules are involved in neuronal degeneration and repair in the CNS, and have been proposed as mediators of various neuropathologies [83—85]. Therefore, many of the clinical and histological effects of HIV-1 infection in the CNS may be an indirect effect of cytokines and other soluble mediators secreted by resident macrophages and microglial cells. There is evidence of increased synthesis of neopterin, a marker of both macrophage activation and tetrahydrobiopterin biosynthesis [86]. TNF-α, IL-1, IL-6, INF-γ, 2 microglobulin, and neopterin are potential candidates serving as neurotoxic factors [48].

Regulatory role for astrocytes in IV-1-mediated encephalopathy. HIV-1-infected brain macrophages participate in neurologic dysfunction through their continual secretion of neurotoxins. The control of macrophage secretory activities was found linked to the astrocytes, a cells that suppressed neurotoxins production and regulate the extent of disease [87]. Benveniste et al. [88] investigated the ability of the major envelope glycoprotein of HIV, *gp120*, to regulate intercellular adhesion molecule-1 (ICAM-1) expression in glial cells. Their results indicate that *gp120* enhances ICAM-1 gene expression in primary rat astrocytes, primary human astrocytes, a human astroglioma cell linc CRT, and primary rat microglia. ICAM-1 is important in mediating immune responsiveness in the CNS, facilitating entry of HIV-infected cells into the CNS, and promoting syncytia formation.

Astrocytes are the most numerous of the glial cells, and in the mammalian brain they outnumber neurons 10 to 1. Astrocytes have been implicated in a wide range of supportive functions for their partner neurons in the CNS, such as neuronal guidance during development and nutritional and metabolic support throughout life [89]. Astrocytes have also been suggested to provide neurotrophic factors essential for neuronal maintenance and survival [90, 91]. The ionic composition of the extracellular space around the neurons is critical for their proper functioning, and the astrocyte is important in maintaining this microenvironment. Numerous studies have demonstrated the active involvement the astrocytes in neurotransmitter metabolism. *In vitro* studies suggest that amino acid transmitters may be removed from the extracellular space by astrocytic uptake mechanisms. In the presence of high glutamate levels, removal of astrocytes from mixed cultures quickly leads to neuronal death [92, 93]. It has been shown that glutamate, a good substrate for the uptake system, is 1/40—1/100-fold weaker as a neurotoxin in astrocyte-rich cultures than in astrocyte-poor cultures [94]. The astrocyte can contribute to the structural integrity of the blood-brain barrier. In the adult nervous system, astrocytes retain the ability to divide and multiply. When the CNS is injured, astrocytes respond by becoming reactive. This reaction, known as astrocytosis is the result of astrocyte proliferation, hypertrophy, and enhanced expression of glial fibrillary acidic protein (GFAP), whose expression is restricted to astrocytes. One of the major functions proposed for reactive astrocytes is the initiation of immune responses within the CNS [37, 44,]. Prominent reactive astrocytosis is seen in AIDS-dementia complex [95].

І. С. Магура, О. М. Рожманова

Роль макрофагів і астроцитів у механізмах нейродегенерації, викликаної інфікуванням ВІЛ-1

Резюме

При захворюванні на СНІД у значної кількості хворих відбувається порушення діяльності центральної нервової системи (ЦНС), обумовлене проникненням вірусу імунодефіциту людини 1 (ВІЛ-1) через гематоенцефалічний бар'єр. Це від-

буває ться завдяки здатності ВІЛ-1-інфікованих моноцитів зв'язуватися мікроваскулярним ендотелієм, що визначає наступне проникнення вірусу у тканину мозку. Індукована ВІЛ-1 патологія ЦНС супроводжується вибірковою загибеллю нейронів кори та сітківки, астроцитозом, порушенням мієлінізації нервових волокон. ВІЛ-1 безпосередньо не інфікує нервові клітини. Головну роль у розвитку патології ЦНС відіграє секреція нейротоксинів ВІЛ-1-інфікованими макрофагами. До цих нейротоксинів належать глутамат-подібні нейротоксичні молекули, вільні радикали, цистеїн, фактор активації тромбоцитів, цитокіни, ейкозаноїди, зокрема арахідонова кислота, а також неідентифіковані фактори, що виділяють активовані макрофаги, а також реактивні астроцити. Білки ВІЛ-1, зокрема поверхневий глікопротеїн gp120, також можуть пошкоджувати нейрони і змінювати функцію астроцитів. Загибель нейронів у хворих на СНІД у значній мірі може залежити від здатності gp120 обумовлювати надмірну стимуляцію НМДА рецепторів і викликати ексцитотоксичні порушення, а також безпосередньо впливати на астроцити, викликаючи зменшення продукування факторів росту і пригнічуючи транспортування глутамату з міжклітинного середовища.

И. С. Магура, О. М. Рожманова

Роль макрофагов и астроцитов в механизмах нейродегенерации, вызванной инфицированием ВИЧ-1

Резюме

Значительное количество больных СПИДом страдает неврологическими нарушениями, обусловленными проникновением вируса иммунодефицита человека (ВИЧ-1) через гематоэнцефалический барьер. ВИЧ-1-инфицированные моноциты способны связываться микроваскулярным эндотелием, что определяет последующее проникновение вируса в ткань мозга. Индуцированная ВИЧ-1 патология центральной нервной системы (ЦНС) сопровождается избирательной гибелью нейронов нейрокортекса и сетчатки, астроцитозом, нарушением миелинизации нервных волокон. ВИЧ-1 непосредственно не инфицирует нервные клетки. Основная роль в развитии патологии ЦНС принадлежит секреции нейротоксинов ВИЧ-1-инфицированными макрофагами. К этим нейротоксинам относятся глутамат-подобные нейротоксические молекулы, свободные радикалы, цистеин, фактор активации тромбоцитов, цитокины, эйкозаноиды, а также неидентифицированные факторы, выделяющие активированные макрофаги и реактивные астроциты. Белки ВИЧ-1, в частности поверхностный гликопротеин gp120, также могуть повреждать нейроны и изменяють функцию астроцитов. Гибель нейронов у больных СПИДом в значительной степени может зависеть от способности gp120 обусловливать избыточную стимуляцию НМДА рецепторов и вызывать экситотоксические нарушения, а также непосредственно влиять на астроциты, вызывая уменьшение продукции факторов роста и угнетая транспорт глутамата из межклеточной среды.

REFERENCES

1. *Miedema F., Klein M. R.* AIDS pathogenesis: a finite immune response to blame? // Science.—1996.—**272**.—P. 505—506.
2. *Freed E. O., Martin M. A.* The role of human immunodeficiency virus type 1 envelope glycoproteins in virus infection // J. Biol. Chem.—1995.—**270**.—P. 23883—23886.
3. *Morrow C. D., Park J., Wakefield J. K.* Viral gene products and replication of the human immunodeficiency type 1 virus // Amer. J. Physiol.—1994.—**266**.—P. C1135—C1156.
4. *Cohen J.* Likely HIV cofactor found // Science.—1996.—272.—P. 809—810.
5. *Feng Y., Broder C. C., Kennedy P. E., Berger E. A.* HIV-1 entry cofactor: functional cDNA cloning of a seven-trans-membrane, G protein-coupled receptor // Ibid.—1996.—N 5263.—P. 872—877.
6. *Oravecz T., Pall M., Norcross M. A.* β-Chemokine inhibition of monocytotrophic HIV-1 infection. Interference with a post-binding fusion step // J. Immunol.—1996.—**157**, N 4.—P. 1329—1332.
7. *Schmidtmayerova H., Sherry B., Bukrinsky M.* Chemokines and HIV replication // Nature.—1996.—**387**.—P. 767.
8. *Trkola A., Dragic T., Arthos J. et al.* CD4-dependent, antibody-sensitive interactions between HIV-1 and its co-receptor CCR-5 // Ibid.—**384**.—P. 184—187.
9. *Meltzer M. S., Gendelman H. E.* Mononuclear phagocytes as targets, tissue reservoirs, and immunoregulatory cells in human immunodeficiency virus disease // Curr. Top. Microbiol. and Immunol.—1992.—**181**.—P. 239—263.
10. *Gartner S., Markovitz D. M., Markovitz R. F. et al.* The role of mononuclear phagocytes in HTLV-III/LAV infection // Science.—1986.—**233**.—P. 215—219.
11. *Koenig S., Gendelman H. E., Orenstein J. M et al.* Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy // Ibid.—P. 1089—1092.
12. *Dhawan S., Weeks B. S., Soderland C. et al.* HIV-1 infection alters monocyte interactions with human microvascular endothelial cells // J. Immunol.—1995.—**154**.—P. 422—430.
13. *Nottet H. S. L., Gendelman H. E.* Unraveling the neuroimmune mechanism for the HIV-1-associated cognitive/motor complex // Immunol. Today.—1995.—**16**.—P. 441—450.
14. *Lafrenie R. M., Wahl L. M., Epstein J. S. et al.* HIV-1-*Tat* protein promotes chemotaxis and invasive behavior by monocytes // J. Immunol.—1996.—**157**.—P. 974—977.
15. *Roulstone A., Lin R., Beauparlant P. et al.* Regulation of human immunodeficiency virus type 1 and cytokine gene expression in myeloud cells by NF-kB/Rel transcription factors // Microbiol. Rev.—1995.—**59**.—P. 481—505.
16. *Finnegan A., Roebuck K. A., Nakai B. E. et al.* IL-10 cooperates with TNF-alpha to activate HIV-1 from latently and acutely infected cells of monocyte/macrophage lineage // J. Immunol.—1996.—**156**.—P. 841—851.
17. *Harrison M. J. G., McArthur J. C.* AIDS and neurology.—Edinburg: Churchill-Livingstone, 1995.—200 p.
18. *Masliah E. In vivo* modeling of HIV-1 mediated neurodegeneration // Amer. J. Pathol.—1996.—**149**.—P. 745—750.
19. *Masliah E., Achim C.L., Ge N. et al.* Spectrum of human immunodeficiency virus-associated neocortical damage // Ann. Neurol.—1992.—**32**.—P. 321—329.
20. *Wiley C. A., Achim C.* HIV encephalitis is the pathologic correlate of dementia in AIDS // Ibid.—1994.—**36**.—P. 673—676.
21. *Navia B. A., Jordan B. D., Price R. W.* The AIDS dementia complex. 1. Clinical features // Ibid.—1986.—**19**.—P. 517.
22. *Price R. W., Sidtis J., Rosenblum M.* The AIDS dementia complex: some current questions // Ibid.—1988.—**23**.—P. S27—S33.
23. *Kure K., Lyman W. D., Weidenheim K. M. et al.* Cellular localization of an HIV-1 antigen in subacute AIDS encephalitis using an improved double-labeling immunohistochemical method // Amer. J. Pathol.—1990.—**136**.—P. 1085—1092.
24. *Wiley C. A., Schrier R. D., Nelson J. A. et al.* Cellular localization of human immunodeficiency virus infection within the brain of acquire immune deficiency syndrome patients // Proc. Nat. Acad. Sci. USA.—1986.—**83**.—P. 7089—7093.
25. *Kure K., Llena J. F., Lyman W. D et al.* Human immunodeficiency virus-1 infection of the nervous system. An autopsy study of 268 adult, pediatric, and fetal brains // Hum. Pathol.—1991.—**22**.—P. 700—710.

26. *Budka H.* Neuropathology of human immunodeficiency virus infection // Brain Pathol.—1991.—**1**.—P. 163—165.
27. *Gray F., Haug H., Chimelli L. et al.* Prominent cortical atrophy with neuronal loss as correlate of human immunodeficiency virus encephalopathy // Acta neuropathol.—1991.—**82**.—P. 229—233.
28. *Weis S., Haug H., Budka H.* Neuronal damage in the cerebral cortex of AIDS brains: a morphometric study // Ibid.—1993.—**85**.—P. 185—189.
29. *Masliah E., Ge N., Achim C. L. et al.* Patterns of neurodegeneration in HIV encephalitis // NeuroAIDS.—1996.—**1**.—P. 161—173.
30. *Everall I. P., Luther P. J., Lantos P. L.* Neuronal loss in the frontal cortex in HIV infection // Lancet.—1991.—**337**.—P. 1119—1121.
31. *Ketzler S., Weis S., Haug H., Budka H.* Loss of neurons in the frontal cortex in AIDS brains // Acta neuropathol.—1990.—**80**.—P. 92—94.
32. *Wiley C. A., Maslaih E., Morey M. et al.* Neocortical damage during HIV infection // Ann. Neurol.—1991.—**29**.—P. 651.
33. *Tenhula W. N., Xu S. Z., Madigan M. C. et al.* Morphometric comparisons of optic nerve axon loss in acquired immunodeficiency syndrome // Amer. J. Ophthalmol.—1992.—**15**.—P. 14—20.
34. *Nottet H. S. L. M., Persidsky Y., Sasseville V. G. et al.* Mechanisms for the transendothelial migration of HIV-1-infected monocytes into brain // J. Immunol.—1996.—**156**.—P. 1284—1295.
35. *Lipton S. A., Gendelman H. E.* Dementia associated with the acquired immunodeficiency syndrome // New Engl. J. Med.—1995.—**332**.—P. 934—940.
36. *Lipton S. A.* HIV displays its coat of arms // Nature.—1994.—**367**.—P. 113—114.
37. *Eddleston M., Mucke L.* Molecular profile of reactive astrocytes-implication for their role in neurologic disease // Neuroscience.—1993.—**54**.—P. 15—36.
38. *Piani D., Constam D. B., Fgei K., Fontana A.* Macrophages in the brain: frends or enemies? // NIPS.—1994.—**9**.—P. 80—84.
39. *Giulian D., Vaca K., Noonan C. A.* Secretion of neurotoxins by mononuclear phagocytes infected with HIV-1 // Science.—1990.—**250**.—P. 1593—1596
40. *Takahashi K., Wesselingh S. L., Griffin D. E. et al.* Localization of HIV-1 in human brain using polymerase chain reaction/*in situ* hybridization and immunocytochemistry // Ann. Neurol.—1996.—**39**.—P. 705—711.
41. *Saito T., Sharer L. R., Epstein L. G. et al.* Overexpression of *nef* as a marker for restricted HIV-1 infection of astrocytes in postmortem pediatric central nervous tissues // Neurology.—1994.—**44**.—P. 474—481.
42. *Tornatore C., Chandra R., Berger J. R., Major E. O.* HIV-1 infection of subcortical astrocytes in the pediatric central nervous system // Ibid.—1994.—**44**.—P. 481—487.
43. *Hickey W. F., Kimura H.* Perivascular microglial cells of the CNS are bone marrow-derived and present antigen *in vivo* // Science.—1988.—**239**.—P. 290—292.
44. *Benveniste E. N.* Inflammatory cytokines within the central nervous system: sources, function, and mechanism of action // Amer. J. Physiol.—1992.—**263**.—P. C1—C16.
45. *Kreutzberg G. V.* Microglia: a sensor for pathological events in the CNS // Trends Neurosci.—1996.—**19**.—P. 312—318.
46. *McGeer P. L., Kawamata T., Walker D. G. et al.* Microglia in degenerative neurological disease // Glia.—1993.—**7**.—P. 84—92.
47. *Flaris N. A., Densmore T. L., Molleston M. C., Hickey W. F.* Characterization of microglia and macrophages in the central nervous system of rats: definition of the differential expression of molecules using standard and novel monoclonal antibodies in normal CNS and in four models of parenchymal reaction // Ibid.—1993.—**7**.—P. 34—50.
48. *Weis S., Neuhaus B., Mehraein P.* Activation of microglia in HIV-1 infected brains is not dependent on the presence of HIV-1 antigens // NeuroReport.—1994.—**5**.—P. 1514—1516.
49. *Brenneman D. E., Westbrook G. L., Fitzgerald S. P. et al.* Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide // Nature.—1988.—**335**.—P. 639—642.
50. *Dreyer E. B., Kaiser P. K., Offermann J. T., Lipton S. A.* HIV-1 coat protein neurotoxicity prevented by calcium channel antagonists // Science.—1990.—**248**.—P. 364—367.
51. *Lipton S. A., Sucher N. J., Kaiser P. K., Dreyer E. B.* Synergistic effects of HIV coat protein and NMDA receptor-mediated neurotoxicity // Neuron.—1991.—**7**.—P. 111—118.
52. *Muller W. E. G., Schrsymbol}der H. C., Ushijima H. et al.* *gp120* of HIV-1 induced apoptosis in rat cortical cell cultures: prevention by memantine // Eur. J. Pharmacol.—1992.—**226**.—P. 209—214.
53. *Savio T., Levi G.* Neurotoxicity of HIV coat protein *gp120*, NMDA receptors, and protein kinase C: a study with rat cerebellar granule cell cultures // J. Neurosci. Res.—1993.—**34**.—P. 265—272.
54. *Lipton S. A.* Requirement for macrophages in neuronal injury induced by HIV envelope protein *gp120* // NeuroReport.—1992.—**3**.—P. 913—915.
55. *Aggoun-Zouaoui D., Charriaut-Marlangue C., Rivera S. et al.* The HIV-1 envelope protein *gp120* induces neuronal apoptosis in hippocampal slices // Ibid.—1996.—**7**.— P. 433—436.
56. *Toggas S. M., Masliah E., Rockenstein E. M. et al.* Central nervous system damage produced by expression of the HIV-1 coat protein *gp120* in transgenic mice // Nature.—1994.—**367**.—P. 188—193.
57. *Lipton S. A.* HIV displays its coat of arms // Ibid.—1994.—**367**.—P. 113—114.
58. *Lipton S. A.* Models of neuronal injury in AIDS: another role for the NMDA receptor? // Trends Neurosci.—1992.—**15**.—P. 7—79.
59. *Dawson V. L., Dawson T. M., Uhl G. R., Snyder S. H.* Human immunodeficiency virus type 1 coat protein neurotoxicity mediated by nitric oxide in primary cortical cultures // Proc. Nat. Acad. Sci. USA.—1993.—**90**.—P. 3256—3259.
60. *Collingridge G. L., Singer W.* Excitatory amino acids and synaptic plasticity // Trends Pharmacol. Sci.—1990.—**11**.—P. 290—296.
61. *Bliss T. V., Collingridge G. L.* A synaptic model of memory: long term potentiation in the hippocampus // Nature—1993.—**361**.—P. 31—39.
62. *Beal M. F., Hyman B. T., Koroshetz W.* Do defects in mitochondrial energy metabolism underline the pathology of neurodegenerative diseases? // Trends Neurosci.—1993.—**16**.—P. 125—131.
63. *Beal M. F.* Mechanisms of excitotoxicity in neurologic disease // FASEB J.—1992.—**6**.—P. 3338—3344.
64. *Schulz J. B., Henshaw D. R., Siwek D. et al.* Involvement of free radicals in excitotoxicity *in vivo* // J. Neurochem.—1995.—**64**.—P. 2239—2247.
65. *Lipton S. A., Choi Y.-B., Pan Z.-H. et al.* A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds // Nature.—1993.—**364**.—P. 626—632.
66. *Dawson V. L., Dawson T. M., Bartley D. A. et al.* Mechanisms of nitric oxide-mediated neurotoxicity in primary brain cultures // J. Neurosci.—1993.—**13**.—P. 2651—2661.

67. *Koprowski H., Zheng Y. M., Heber-Katz E. et al.* In vivo expression of inducible nitric oxide synthase in experimentally induced neurologic diseases // Proc. Nat. Acad. Sci. USA.—1993.—90.—P. 3024—3027.
68. *Bukrinsky M. I., Nottet H. S. L. M., Schmidtmayerova H. et al.* Regulation of nitric oxide synthase activity in human immunodeficiency virus type 1 (HIV-1)-infected monocytes: implications for HIV-associated neurological disease // J. Exp. Med.—1995.—18.—P. 735—745.
69. *Lipton S. A.* Prospects for clinically tolerated NMDA antagonists: open-channel blockers and alternative redox states of nitric oxide // Trends Neurosci.—1993.—16.—P. 527—532.
70. *Lee S. C., Dickson D. W., Liu W., Brosnan C. F.* Induction of nitric oxide synthase activity in human astrocytes by interleukin-1 β and interferon γ // J. Neuroimmunol.—1993.—46.—P. 19—24.
71. *Pietraforte D., Tritarelli E., Testa U., Minetti M. gp120* HIV envelope glycoprotein increases the production of nitric oxide in human monocyte-derived macrophages // J. Leukocyte Biol.—1994.—55.—P. 175—182.
72. *Munir M., Lu L., McGonigle P.* Excitotoxic cell death and delayed rescue in human neurones derived from NT2 cells // J. Neurosci.—1995.—15.—P. 7847—7860.
73. *Wu P., Price P., Du B. et al.* Direct cytotoxicity of HIV-1 envelope protein *gp120* on human NT neurons // NeuroReport.—1996.—7.—P. 1045—1049.
74. *Robbins D. S., Shirazi Y., Drysdale B. E. et al.* Production of cytotoxic factors for oligodendrocytes by stimulated astrocytes // J. Immunol.—1987.—139.—P. 2593—2597.
75. *Wahl S. M., Allen J. B., McCartney-Francis N. et al.* Macrophage- and astrocyte-derived transforming growth factor beta as a mediator of central nervous system disfunction in acquired immune deficiency syndrome // J. Exp. Med.—1991.—173.—P. 981—991.
76. *Gallo P., Frei K., Rordorf C. et al.* Human immunodeficiency virus type 1 (HIV-1) infection of the central nervous system: an evaluation of cytokines in cerebrospinal fluid // J. Neuroimmunol.—1989.—23.—P. 109—116.
77. *Merril J. E., Martinez-Maza O.* Cytokines in AIDS-associated neurons and immune system disfunction // Neurobiology of cytokines. P B; Methods in neuroscience / Ed. DeSouza E. B.—San Diego: Acad. press, 1993.—P. 243—266.
78. *Tyor W. R., Glass J. D., Griffin J. W. et al.* Cytokine expression in the brain during the acquired immunodeficiency syndrome // Ann. Neurol.—1992.—31.—P. 349—360.
79. *Selmaj K. W., Raine C. S.* Tumor necrosis factor mediates myelin and oligodendrocyte damage *in vitro* // Ibid.—1988.—23.—P. 339—346.
80. *Griffin W. S. T., Stanley L., Ling C. et al.* Brain interleukin-1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer's disease // Proc. Nat. Acad. Sci. USA.—1989.—86.—P. 7611—7615.
81. *Gelbard H. A., Nottet H. S. L. M., Swindells S. et al.* Platelet-activating factor: a candidate human immunodeficiency virus type 1-induced neurotoxin // J. Virol.—1994.—68.—P. 4628—4635.
82. *Genis P., Jett M., Bernton E. W. et al.* Cytokines and arachidonic metabolites produced during human immunodeficiency virus (HIV)-infected macrophage-astroglia interactions: implications for the neuropathogenesis of HIV disease // J. Exp. Med.—1992.—176.—P. 1703—1718.
83. *Merrill J. E., Benveniste E. N.* Cytokines in inflammatory brain lesions: helpful and harmful // Trends Neurosci.—1996.—19.—P. 331—338.
84. *Hopkins S. J., Rothwell N. J.* Cytokines and the nervous system I: expression and recognition // Ibid.—1995.—18.—P. 83—87.
85. *Rothwell N. J., Hopkins S. J.* Cytokines and the nervous system II:actions and mechanisms of action // Ibid.—P. 130—136.
86. *Sakai N., Kaufman S., Milstien S.* Parallel induction of nitric oxide and tetrahydrobiopterin synthesis by cytokines in rat glial cells // J. Neurochem.—1995.—65.—P. 895—902.
87. *Nottet H. S. L. M., Jett M., Flanagan C. R. et al.* Regulatory role for astrocytes in HIV-1 encephalitis: an overexpression of eicosanoids, platelet-activating factor, and tumor necrosis factor-α by activated HIV-1-infected monocytes is attenuate by primary human astrocytes // J. Immunol.—1995.—154.—P. 3567—3561.
88. *Shrikant P., Benos D. J., Tang L. P., Benveniste E. N.* HIV glycoprotein 120 enhances intercellular adhesion molecule-1 gene expression in glial cells // Ibid.—1996.—156.—P. 1307—1314.
89. *Shao Y., McCarthy K. D.* Plasticity of astrocytes // Glia.—1994.—11.—P. 147—155.
90. *Rudge J. S.* Astrocyte-derived neurotrophic factors // Astrocytes: pharmacology and function / Ed. S. M. Murphy.—New York: Academia, 1993.—P. 267—305.
91. *Mattson M. P., Cheng B., Smith-Swintosky V. L.* Mechanisms of neurotrophic factor protection against calcium- and free radical-mediated excitotoxic injury: implications for treating neurodegenerative disorders // Exp. Neurol.—1993.—124.—P. 89—95
92. *Sugiyama K., Brunori A., Mayer M. L.* Glial uptake of excitatory amino acids influences neuronal survival in cultures of mouse hippocampus // Neuroscience.—1989.—32.—P. 779—791.
93. *Rosenberg P. A., Amin S., Leitner M.* Glutamate uptake disguises neurotoxic potency of glutamate agonists in cerebral cortex in dissociated cell culture // J. Neurosci.—1992.—12.—P. 56—61.
94. *Rosenberg P. A., Aizenman E.* Hundred-fold increase in neuronal vulnerability to glutamate toxicity in astrocyte-poor cultures of rat cerebral cortex // Neurosci. Lett.—1989.—103.—P. 162—168.
95. *De La Monte S. M., Ho D. D., Schooley R. T. et al.* Subacute encephalomyelitis of AIDS and its relation to HTLV-III infection // Neurology.—1987.—37.—P. 562—569.

Received 11.12.96