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Neurotransmission in HIV associated dementia: a short review

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Summary. Human immunodeficiency virus (HIV) infection is frequently associated with specific neurological and psychiatric symptoms. Our understanding of how HIV-related CNS deficits develop is still preliminary and the cause remains obscure. However, some clues have emerged which may clarify uncertainties. Following a brief discussion of the epidemiology underlying neuropathological mechanisms and clinical symptoms in HIV-infected patients, we focus our attention on neurochemical data obtained by studies in humans and rhesus monkeys which provide information on the effect of the retroviral infection on neurotransmission and assist in the evaluation of potential therapeutic treatments.

Keywords: HIV, SIV, neurotransmission, dementia, dopamine, glutamate, acetylcholine.

Epidemiology and clinical signs of HIV associated dementia

The Acquired Immunodeficiency Syndrome (AIDS) continues to spread around the world being one of the 10 leading causes of death (Masliah et al., 1996). According to WHO report on the global human immunodeficiency virus (HIV)/AIDS pandemic, June 2000, nearly 35 million adults and 2 million children worldwide are infected with HIV and it is estimated that one third of the adults and more than one half of the children will develop a dementing illness. HIV is the leading cause of dementia in people less than 60 years of age (Janssen et al., 1992; McArthur et al., 1993). The clinical prognosis of dementia is very poor; people die on average six months after onset of dementia (Harrison and McArthur, 1995).

HIV associated dementia is characterized by psychiatric and neurological symptoms including cognitive dysfunction, behavioural abnormalities and motor disorders which are attributed to HIV infection per se rather than being associated with subsequent opportunistic infections or malignancies (Price,

1996). Effective medication has recently lowered the rates of dementia but it also has extended survival of people with HIV so that they become more vulnerable for developing dementia in the future (Lopez et al., 1999).

In the early stages of HIV associated dementia, clinical neurological findings are subtle and include mental and physical slowing (Navia et al., 1986). These symptoms may progress, usually in months to forgetfulness and behavioural changes. Patients typically report difficulties with carrying out simple daily living activities. Serious memory loss, apathy and depression usually follow (Navia et al., 1986). Neurologically, they may have an abnormal gait, tremor, and bradykinesia (Navia et al., 1986). As dementia advances, memory deteriorates and the patients may exhibit language disorders. The terminal stage of dementia is characterized by global cognitive impairment and severe psychomotor retardation. Progression to a florid dementia with incontinence, hallucinations, seizures and coma is characteristic at or near the time of death (Navia et al., 1986). The severity of cognitive and motor impairment can be staged using the Memorial Sloan-Kettering (MSK) scale which assesses patients functional impairment. The MSK scale ranges from mild dementia or minimal cognitive and motor deficits (MSK = 1) to severe dementia or and vegetative stage (MSK = 4) (Price et al., 1988).

Neurotransmitter systems in HIV associated dementia

The pathogenesis of HIV-mediated brain impairment has remained unclear and efforts to determine the underlying cause of the neuronal dysfunction is complicated due to the absence of direct viral infection of neurons (Takahashi et al., 1996). So far, it is greatly accepted that HIV induces a neuropathological process through indirect toxicity on neurons (Glass and Johnson, 1996). The current opinion is that secreted toxic factors by infected cells including proinflammatory cytokines, neopterin, arachidonic acid, glutamate and quinolinic acid may underlie the neurodegenerative processes associated with the HIV-induced dementia. These toxins may affect the neurotransmitters regulations, impair adaptive mechanisms and lead to cell loss via excitotoxic mechanisms. In this article we will review the basic neurotransmitter systems involved in HIV associated dementia to provide an insight into the neurochemistry underlying clinical symptoms in HIV infection and therefore to support the reader with basic information for a rational development of a treatment strategy for the future.

Amino acid neurotransmission in HIV associated dementia

The intriquing possibility that excitatory amino acids are implicated in HIV associated dementia has gained increasing interest in recent years; in vitro and in vivo experiments indicate that the viral proteins gp 120 and Tat may cause neuronal apoptosis which can be blocked by receptor antagonists for which excitatory neurotransmitters such as glutamate can act as a substrate (Nath and Geiger, 1998; Lipton et al., 1991). This evidence suggests that the glutamatergic system and excitotoxicity are involved in the pathogenesis of HIV associated dementia. However, viral proteins do not bind to glutamate

receptors, so that overstimulation of glutamate receptors seems to be mediated by interactions with endogenous glutamate or other excitatory amino acid receptor agonists. Studies in the periphery reported that plasma glutamate concentrations are highly elevated in all groups of HIV-positive patients, including those without overt symptoms (Droge et al., 1987). Increased CSF glutamate levels were reported in AIDS patients (Ferrarese et al., 1997). This increase was suggested to be consistent with impaired glial uptake induced by gp 120 (Ferrarese et al., 1997) or elevated plasma glutamate in AIDS patients (Gurwitz and Kloog, 1997). A longitudinal assessment of the concentration of amino acid neurotransmitters in CSF of SIV-infected monkeys demonstrated an increase in the concentration of the excitatory amino acid neurotransmitter glutamate, but not aspartate, starting at 11 weeks post-infection, with a parallel decrease of the inhibitory neurotransmitter GABA (Koutsilieri et al., 1999). Moreover, it was shown, in contrast to the belief so far, that the increase in glutamate may be originated by microglia and correlated with high levels of viral antigen. In post-mortem brains of HIV-demented patients, a reduction of the NMDA receptor density was shown, suggesting a downregulation of receptor synthesis following a chronic overstimulation (Sardar et al., 1999). Among the other excitatory amino acid receptor agonists potentially involved in HIV associated dementia, the endogenous metabolite of L-tryptophan quinolinic acid, seems to be very interesting. HIV-infected patients show early and sustained increases in CSF quinolinic acid levels (Heyes et al., 1989). CSF elevated quinoline concentration has been shown to correlate with the severity of dementia in late stages HIV-infected patients (Heyes et al., 1991), and in SIV-infected macaques with overt neurological symptoms (Heyes et al., 1992; Rausch et al., 1994). Quinolinic acid is produced by macrophages (Heyes et al., 1992), suggesting that macrophage infiltration into the brain may contribute to increased brain quinolinic acid levels and thereby be a major contributor to early CNS impairment.

Demonstration of the role of glutamate and other excitotoxins in HIV-infected patients will help to direct the research for neuroprotective therapies with NMDA-antagonists such as memantine available now for clinical trials.

Dopamine systems in HIV associated dementia

AIDS patients with HIV associated dementia have many clinical signs in common with Parkinsonian features (Lopez et al., 1999; Nath et al., 2000). These may include apathy, bradyphrenia, bradykinesia, impaired manual dexterity, postural instability, gait abnormalities, rigidity, hypomimetic facies and hypophonic and poorly articulated speech (Navia et al., 1986; Currie et al., 1988). Further, autopsy studies of patients with AIDS have described HIV-infected macrophages and multinucleated cell infiltrates in the dopamine-rich basal ganglia (Navia et al., 1986). Using [^{18}F]fluorodeoxyglucose PET imaging, it could be shown that there is a hypermetabolism of the subcortical structures such as basal ganglia in the early stages of HIV-induced dementia. Among the more advanced patients there was cortical and subcortical gray matter hypometabolism (Rottenberg et al., 1996).

An important early clue to the involvement of the dopaminergic system in HIV infection is the exquisite sensitivity to dopamine receptor antagonists in HIV-infected patients and appearance of extrapyramidal manifestations (Hriso et al., 1991; Hollander et al., 1985; Edelstein and Knight, 1987). This hypersensitivity to dopamine receptor blockade was attributed to an alteration in dopaminergic systems (Hriso et al., 1991).

There have been a few studies that have measured CSF biogenic amines. It has been demonstrated that CSF homovanillic acid levels (HVA) were diminished in patients with AIDS and more severely in patients with AIDS dementia (Kramer and Sanger, 1990; Larsson et al., 1991; Sofic et al., 1992; Berger et al., 1994). In SIV-infected monkey model, CSF 3,4-dihydroxyphenylacetic acid (DOPAC) increased after 8 months infection compared to control animals, suggesting an increase in dopamine synthesis. In contrast, HVA, the main metabolite of dopamine remained unchanged (Koutsilieri et al., 1997b). Previous studies have shown that CNS monoamine metabolite levels are closely associated with indices of regional CNS transmitter turn over, although not all regions are well reflected in the CSF concentration (Goldman-Rakic and Brown, 1981). Thus, while CSF metabolite levels may reflect the overall activity of CNS dopaminergic systems, the determination of the activity of specific anatomical regions remains limited using this assessment. One post-mortem study was performed in the caudate of AIDS patients, including a group exhibiting dementia, and reported reduction of dopamine and its metabolites (Sardar et al., 1996). A surprising evidence for an early dopamine reduction, following 8–20 weeks post infection, comes from SIV-infected monkeys (Czub et al., 2001). These data provided the first direct evidence for a decrease in dopamine levels already two to three months post infection, in the early asymptomatic phase (Czub et al., 2001). Dopamine levels were reduced in putamen, hippocampus and frontal cortex of SIV-infected animals. The substantia nigra, a region rich in dopaminergic cell bodies showed no dopamine loss, indicating that the virus or viral products affect initially dopaminergic terminals in the postsynaptic dopaminergic areas. In contrast, in human post-mortem studies, brains of HIV-infected subjects exhibited marked neuronal degeneration in the substantia nigra (Itoh et al., 2000). Whether a further retrograde degeneration of the dopaminergic projections will accompany late stages of SIV infection remains to be elucidated.

Surprisingly, in the SIV-macaques, enhanced dopamine availability, following neuropharmacological treatment, caused marked degenerative CNS changes and accelerated SIV infection (Czub et al., 2001), suggesting dopamine dysregulation as a pathogenetic factor for NeuroAIDS. Further, dopaminergic treatment resulted in a significant increase in SIVmRNA-expressing cells compared with the number in SIV-infected/untreated animals (Czub et al., 2001). The enhanced availability of dopamine effected by dopaminergic drugs such as selegiline and L-DOPA accounts for the symptomatic benefit of these drugs in Parkinson's disease, characterized by a regional reduction in dopamine levels. However, increased dopamine availability in the presence of a retroviral infection of the CNS is associated with the induction of neuropathology rather than neuroprotection. In accordance, in another immuno-

deficiency virus cat model, methamphetamine, a dopaminergic drug, increased the viral replication (Phillips et al., 2000).

In vitro, dopamine was shown to have a toxic potential on HIV-exposed neuronal cells and to be involved in the regulation of HIV gene expression in neuronal cells and cells of the immune system (Sawaya et al., 1996; Rohr et al., 1999; Koutsilieri et al., 1997a). Moreover, dopamine markedly activated HIV in chronically-infected T lymphoblasts (Scheller et al., 2000). This finding was associated with oxidative stress since glutathione and its precursor N-acetylcysteine totally inhibited the effect of dopamine (Scheller et al., 2000).

It is obvious from the discussion above, that the dopaminergic system is greatly involved in HIV associated dementia, not only due to a vulnerability to the effects of the virus but as a possible pathogenetic factor for the development of the infection.

The cholinergic system in HIV associated dementia

Cognitive impairment in the subclinical stages of HIV infection is not widespread or a requisite feature of HIV infection, although studies report neuropsychological deficits in pre-AIDS patients (McArthur et al., 1989). Early signs of cognitive deficits in HIV-infected humans may be dominated by impairment in attentional functions which results in the end in reduction in perceptual and psychomotor speed (Sarter and Podell, 2000). Several lines of evidence have strongly supported the crucial role of cortical cholinergc inputs in the mediation of attentional functions including the regulation of processing capacity (Sarter et al., 1996). However, examination of the brains of HIV-infected subjects has not been focusing on the integrity of neurochemically defined systems and therefore, information about the status of the cholinergic system in HIV dementia is unavailable. In contrast, in SIV-infected monkeys reduced cholinergic neurotransmission was shown in form of a dramatically reduced activity of choline acetyltransferase (ChAT), the enzyme responsible for the biosynthesis of acetylcholine (Koutsilieri et al., 2000). ChAT, is presently the most specific indicator to monitor the functional state of cholinergic neurons in the CNS (Oda, 1999), and one of the most used estimates of cognitive dysfunction. Significant positive correlations were found in humans between ChAT levels and neuropsychological such as the Mini-Mental State Examination and the Logical Memory subtest of the Wechsler Memory Scale (Baskin et al., 1999). ChAT activity was dramatically reduced in putamen and hippocampus of SIV-infected monkeys already during asymptomatic infection without a correlation to brain viral load or CNS pathological lesions (Koutsilieri et al., 2000). The very early impairment of the cholinergic system, indicative of a cognitive dysfunction and independent initially of the viral burden indicates rather deficits associated with global immunological and neurochemical changes than to discrete virus induced pathological lesions. ChAT activity was totally restored following treatment with selegiline, at doses at which the drug possesses dopaminergic properties (Koutsilieri et al., 2001). Selegiline is currently used as anti-dementia substance in HIV associated dementia (Dana Consortium, 1998). The involvement in therapeutical

trials has been attributed so far to its general neuroprotective features. It is obvious, however, from the above study that selegiline may act on the cholinergic system by modulating choline acetyltransferase activity suggesting this mechanism to be the responsible for the anti-dementia effects on humans. However, selegiline as discussed above may accelerate the development of the retroviral infection. A careful consideration of the advantages and disandvantages of a therapeutic approach with dopaminergic drugs on impaired cognition in HIV associated dementia is required.

Comments

There are many gaps in our understanding of the pathogenesis of HIV associated dementia. Such questions are difficult to answer in the human host because of the difficulty in identifying acutely infected individuals and the inaccessibility of the human brain for sampling during infection. Animal models are a necessary tool to allow us to identify viral virulence factors and the host's responses to infection. SIV infection of macaques results in neurological abnormalities that are clinically and pathologically similar to those of HIV-induced dementia. Macaques can be inoculated with well-characterized virus strains to identify specific viral genes that are important in the development of brain-specific disease. Further, body fluids can be repeatedly sampled and tissues analysed at different stages of disease. Pharmacological treatments can be performed which give information about neurotransmitter systems and the therapeutic profile in the brain.

A careful analysis and correlations of neurochemical, pharmacological, pathological and virological data obtained in the SIV monkeys are required in order to enable the reconstruction of a complete picture of the interrelationships between the viral virulence mechanisms and the host's brains reactions and to apply this information in clinical trials in humans.

Future aspects

After the introduction of highly active antiretroviral therapy (HAART) in 1996, the rates of dementia have declined. However, not to the same extent as other AIDS-defining diseases, indicating that viral suppression in the periphery is not sufficient or that additional mechanisms, may be responsible for the brain destruction which have to be defined and treated. In addition, the brain may serve as a reservoir for viral replication under HAART representing a sanctuary where resistances may develop. Therefore, it is expected that HIV associated dementia will be a great problem with time. Our knowledge about changes in the neurotransmitter systems during HIV dementia is still very weak despite the studies in SIV-infected rhesus monkeys. It is indeed this information which is necessary in order to design targeted therapies so that the amelioration of HIV dementia may be possible in the future.

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