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Mechanism of neuropathogenesis

CNS entry The major HIV-1 receptors are CD4 and CD8; various chemokine receptors e.g. CXCR4 and CCR5 are considered as HIV-1 co-receptors. CD4+ helper T lymphocytes are the major routes of multiplication and entry, apart from monocytes. Infected CD4+ T cells and monocytes, which circulate in the blood, are the potential source of CNS infection. The strains of HIV, which are isolated from the brain, have the characteristic of infecting macrophages rather than lymphocytes. Macrophage-tropism is related to a mutation in a specific region of gp120, the external glycoprotein of the virus. In the late stages of the infection, active replication of the virus generates more of these mutants and the compromised immune system permits the escape of these mutants, leading to predominance of macrophage-trophic strains. In order to enter the brain, HIV-1 must cross the BBB using mechanisms that remain unclear. The generally accepted model is the "Trojan Horse hypothesis". HIV enters the CNS as a passenger in cells trafficking to the brain via CD4 T cells or monocytes. Virus accumulation in perivascular regions has been demonstrated as a proof for the above model. An alternative hypothesis of HIV-1 neuro-invasion proposes the entry of free HIV-1 by migration between or, transcytosis of endothelial cells. The mechanism of endothelial infection remains a controversial issue – as CD4 expression in endothelial cells is unclear. Theoretically all the main cell types of the CNS, astrocytes, oligodendrocytes, neurons, perivascular macrophage and microglia, can be infected by HIV-1 since they possess the receptors and/or coreceptors for HIV-1 entry, but only the latter two are the most commonly infected cells by HIV-1. Most studies have indicated an absence of in vivo infection in neurons - It is unclear whether detection of infected neurons is complicated by the loss of the infected neuronal populations. Mechanism of neuropathogenesis Two components of this mechanism are:

1. The direct effect of the HIV-1 infection
2. The indirect consequence of infection comprising the secretion of cytokines and neurotoxins. The infected macrophages and microglia participate actively in the neurodegeneration by: 1) shedding viral proteins and 2) releasing significant amount of

cytokines and neurotoxins into the CNS. 3) Tat and TNF-α contribute to the disruption of the blood-brain barrier, which in turn become more permeable to infected monocytes and cytokines present in the periphery. The secreted pro-inflammatory cytokines activate microglia and astrocytes, which in turn secrete neurotoxins. In addition, the alteration of astrocyte function results in an increase in the level of neurotoxicity in the brain. Neuronal injury via apoptosis is currently believed to be produced by toxic products released directly by HIV-infected macrophages and microglia or by activated astrocytes. Some of these factors have been identified: they include the platelet activating factor, quinolinic acid, nitric oxide, and some

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