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Workshop

HIV-associated neural injury and apoptosis: excitotoxins, chemokines and caspases

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83

Workshop on HIV-associated neural injury and apoptosis: excitotoxins, chemokines, and caspases

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Human immunodeficiency virus-1 (HIV-1) can induce dementia with alarmingly occurrence worldwide. The mechanism of HIV-associated dementia unfortunately, remains poorly understood, but the discovery of HIV-1 binding sites in the brain, including chemokine receptors, has provided new insights. Brain macrophages and microglia, but not neurons, are infected by HIV-1. Mysteriously, however, neurons are injured and may die from apoptosis. The predominant pathway to neuronal injury appears to be indirect via the release of macrophage, microglial and astrocyte toxins that produce overexcitation and free radical formation resulting in excitotoxicity, a process shared with other neurodegenerative diseases. Recent insights into signaling pathways mediating these neurotoxic events offer hope for the development of therapeutic targets. In this Workshop, we will review the pathophysiology of HIV-associated dementia, concentrating on the pathways to neuronal injury involving (i) chemokine receptor activation on the cell surface of macrophages, astrocytes, and neurons, and (ii) caspase activation in neurons, eliciting both mitochondrial and non-mitochondrial apoptotic signals.

84

TNF-a and gp120 induced astroglial dysfunction—implications for HIV-1 associated encephalopathy

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Injurious molecules which are locally released in the CNS play a crucial role in the pathogenesis of HIV-1 associated encephalopathy. These soluble factors include cytokines like TNF-a, and chemokines, secreted by microglia or macrophages but also HIV-1 proteins released from infected cells. They initiate or maintain inflammatory responses within the CNS but may also directly affect functional properties of neurons and astrocytes. Therefore, we studied the effects of TNF-a, chemokines and HIV-1 proteins (gp120, Tat) on electrophysiological membrane properties, i.e., membrane potential and K+ currents, and on intracellular Ca2+ regulation and Ca2+ responses on physiological stimuli. TNF-a induces a depolarization of astrocytes associated with an intracellular Ca2+ increase. The depolarization was due to a protein kinase C dependent reduction of inwardly rectifying K+ currents, the type of K+ current which determines the membrane potential. Other types of K+ currents were not affected. Interestingly, neuronal membrane potential and K+ currents were unaffected. Secondary to the depolarization astroglial Ca2+ responses to glutamate or ATP were reduced. The regulatory HIV-1 protein Tat exerts similar effects and acts synergistically with TNF-a. Various chemokines as well as HIV-1 gp120 elicit an intracellular Ca2+ increase in astrocytes and neurons, which is due to a Ca2+ release from internal stores. Specifically in astrocytes, an intracellular Ca2+ dysregulation is induced with a reduction of glutamate or ATP evoked intracellular Ca2+ increases. Our data suggest that a variety of electrophysiological alterations are induced by cytokines, chemokines and HIV-1 proteins especially in astrocytes and this may contribute to the pathogenesis of HIV-1 associated encephalopathy.

85

Chemokines and their receptors in HIV-associated dementia

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Humans suffering from HIV-associated dementia (HAD) and transgenic mice expressing HIV-1 envelope protein gp120 display similar neuropathological features. Picomolar amounts of recombinant gp120 trigger neuronal apoptosis in mixed neuronal/glial cerebrocortical cultures from humans and rodents. HIV-1 enters into macrophages/microglia or T-cells after binding of its gp120 to chemokine receptors in conjunction with CD4. Whereas T-cells are infected via the chemokine receptor CXCR4 and/or CCR5, macrophages and microglia are primarily infected via CCR5 or CCR3. Chemokine receptors are also present on neurons and astrocytes in the brain, although these cells are not thought to harbor productive infection. In vitro studies suggest that distinct chemokine receptors mediate HIV-associated neuronal damage while others may serve a protective role. Three combinations of chemokine receptors and their respective ligands are of particular interest in HAD: CXCR4 and SDF-1; CCR5 and RANTES or MIP-1alpha/beta; and CX3CR1 and fractalkine. This presentation will review general aspects of

chemokines and their receptors in the neuropathology of HIV infection in combination with recent findings from ongoing research in the field. We observed that in cerebrocortical cultures from CXCR4- and CCR5-deficient mice, neurotoxicity of gp120 is altered depending on the HIV-1 strain from which the envelope protein is derived. The natural ligand of CXCR4, SDF-1, can also induce neuronal apoptosis, whereas, beta-chemokines MIP-1beta and RANTES abrogate the neurotoxicity of gp120 and SDF-1. Neurotoxicity of gp120 involves overstimulation of the NMDA subtype of glutamate receptors, and MIP-1beta provides also partial protection against a direct excitotoxic insult by NMDA. However, inactivation or depletion of microglia prevents only the neurotoxicity of gp120, but not SDF-1. These findings suggest neurotoxic activation of CXCR4 by SDF-1 and a neuroprotective engagement of CCR5 by MIP-1beta directly on neurons or astrocytes rather than solely via microglia. Interestingly, neurotoxicity of gp120 can occur in the absence of either CXCR4 or CCR5 and is mediated predominantly via microglia.

86

Caspase enzymes in HIV induced neuronal injury and apoptosis

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Infection with HIV-1 can result in a syndrome known as HIV-associated dementia (HAD). Neurons are not productively infected by HIV-1; thus, the mechanism of HIV-induced neuronal injury remains incompletely understood. HAD neuropathology includes evidence of dendrite degeneration, synapse loss and apoptosis. The molecular mediators of HIV related neuronal injury might include caspase enzymes. Caspases, a family of proteases with well-described roles in apoptosis, are synthesized as inactive pro-enzymes and activated in a proteolytic cascade after expsure to apoptotic signals. The family is thus subdivided into enzymes acting upstream or downstream in the cascade. To study the cascade of caspase activation involved in HIV mediated neuronal injury, we employed an in vitro model of HIV-induced neuronal apoptosis. Mixed cerebrocortical cultures exposed to the HIV coat protein gp120 demonstrate increased caspase-3 (a downstream caspase) activity. Specific inhibitors of both the Fas/TNF-a/death receptor pathway and the mitochondrial caspase pathway prevent gp120-induced neuronal apoptosis in vitro, suggesting that synergistic activation of multiple upstream caspases is required for gp120 induced neuronal apoptosis. Intra-neuronal expression of a dominant interfering caspase prevents dendrite degeneration in transgenic mice with CNS expression of HIV/gp120. Astrocytosis in the gp120 transgenic mouse is not affected by intra-neuronal caspase inhibition, demonstrating that neuronally generated interleukin-1b is not required for the gp120 induced astrocytic response. These findings suggest that caspase enzymes may mediate sub-apoptotic forms of neuronal injury including dendrite degeneration. Finally, we observed in human postmortem brains that HAD is associated with increased immunoreactivity for the active form of caspase-3. This immunoreactivity is localized to the soma and dendrites of neurons and not limited to neurons with an apoptotic nucleus. These findings suggest that caspases may be activated during a period of neuronal dysfunction, prior to the onset of nuclear apoptosis, and may thus mediate synaptic or dendritic injury associated with HAD.