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Meeting Report

CNS as an HIV-1 reservoir; BBB and Drug Delivery

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In September of last year, the National Institute of Neurological Disorders and Stroke (NINDS) sponsored an AIDS Program Panel meeting entitled 'CNS as an HIV-1 Reservoir: BBB and Drug Delivery'. The main objective of this highly focused meeting was to discuss the latest understandings of systemic drug delivery to the brain and the difficulties which may be associated with developing optimal treatment for HIV-1-associated CNS disorders. To address this issue the participants, which consisted of clinical and basic science experts in AIDS and HIV-1/CNS infection along with vascular cell biologists, pharmacologists and brain tumor biologists, initially had a general discussion on the pathogenesis of HIV-1-induced neurological dysfunction. The participants presented their views in three sessions: NeuroAIDS, the Blood-Brain Barrier (BBB), and drug delivery to the CNS; to attempt to clarify many uncertainties pertaining to current treatment modalities for HIV-1-induced pathology in the brain. Once general concepts of the neuropathogenesis of HIV-1-induced disease were discussed, special effort was made to define the areas of research which require increased attention, such as the identification of efficient mechanisms of CNS drug delivery for the treatment of neurological dysfunction seen in AIDS patients.

The current model as to how HIV-1 infection of the CNS occurs was acknowledged. According to this model, the virus may either access the CNS through trafficking of infected leukocytes into the brain, and/or through transfer of the virus via the brain endothelium. In addition to microglia, the major viral reservoir in the CNS, restricted infection of astrocytes and brain endothelial cells was further emphasized. It was noted that HIV-1 strains present in CNS-specific cellular targets are genetically distinct from those in the periphery. It is the CNS variants that may develop resistance to current antiviral therapies as a result of a sub-optimal level of pharmacological agents in the brain, which in turn, may provide a reservoir of virus in the brain. Much focus was given to the significance of studying chemokine receptors as attachment sites for HIV-1. It was noted that neurons contain such receptors, however since the infection of neurons by HIV-1 is still uncertain, it remains unclear as to how expression of such receptors relates to earlier reports of limited, if any, infection of neurons in the AIDS brain. On a different note, it was also suggested that chemokines and their receptors may be involved in mediating the influx of infected macrophages into the CNS. In light of the high degree of diversity in these classes of receptors, further study is required to decipher their direct and indirect roles in HIV-1-induced CNS pathology. Nevertheless, the current data suggest that viral receptors and co-receptors may serve as potential targets for the development of therapeutic strategies against HIV-1 in brain.

With regard to the BBB and drug delivery, experts on cerebral vasculature commented on the complex nature of BBB integrity and the effect of HIV-1 infection on BBB permeability in infected individuals. Earlier observations have noted an enhanced permeability of the BBB in HIV-1 subjects based on the detection of increased levels of serum proteins, evidence of inflammation of the brain parenchyma, and an increase in the expression of cell adhesion molecules in the brain. However, neuroimaging studies have failed to support these observations. It was, therefore, suggested that BBB permeability should be tested with compounds such as dextran-coated iron conjugates through the use of animal models in order to clarify this important issue. Several *in vitro* models of the BBB were presented with special emphasis on perturbation of its integrity by HIV-1. Although some appear to represent suitable *in vitro* models, correlation of the *in vitro* findings is limited due to the acute nature of changes in the *in vitro* models as opposed to chronic changes *in vitro*.

Another topic that attracted a great deal of attention was the delivery of therapeutic drugs across the BBB. There was a consensus among the participants that HIV-1 within the CNS may be protected from the currently used highly aggressive anti-retroviral therapy (HAART). It was emphasized that assessment of the viral load and the presence of

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anti-viral agents in the CSF should not be used as a measure of such indicators in the CNS. In addition, since viruses isolated from the periphery, CSF, and brain display genetic variations, these compartments should be considered as independent entities. While systemic drug therapy has shown a measure of success, and therapeutic levels of such drugs have been achieved in the CSF, the CNS may still remain inaccessible to such compounds. As such, the CNS may become a sanctuary site for the virus which, in turn, can then be delivered back to the periphery. It was, therefore, suggested that the information obtained through the analysis of CSF should be evaluated in light of data from brain tissues of the affected patients in order to define the status of the disease and the virus in CNS cells. The use of animal models in correlative studies which compare the viral load and quasispecies in periodically sampled plasma and CSF with those from brain and other relevant tissues was further recommended.

Several discussions addressed neuronal injury and cell death associated with HIV-1 infection as convincingly demonstrated using *in vivo* MR spectroscopic studies. In such studies, however, the connection between BBB dysfunction and neuronal injury have remained unexplored. One of the proposed approaches to facilitate drug delivery was to concentrate efforts on a better understanding of the components of the BBB. This could perhaps be achieved by establishing a database to assist in the identification of key vascular components of the BBB including receptors, ligands, and transporter systems. It was emphasized that HIV-1 protease inhibitors, due to their large molecular weight and their characteristic water solubility, may not be transported across the BBB in pharmacologically significant quantities. Recent studies have suggested that these compounds serve as substrates for P-glycoprotein and related multidrug resistant gene proteins within the BBB. Studies have suggested the utilization of P-glycoprotein inhibitors capable of crossing brain capillary endothelium, as P-glycoprotein is selectively expressed at the astrocyte foot processes of the human brain microvasculature, in order to increase brain uptake of protease inhibitors. Among the proposed means to deliver therapeutic agents were the use of liposome technology and chimeric peptide technology. In addition, controlled paracellular diffusion of anti-viral agents through pharmacological opening and closing of tight junctions was recommended. Another important point was based on the notion that although viral load has proven essential for the development of therapy in the periphery, due to the indirect pathways involved in HIV-1 CNS injury, correlation of viral load with the severity of CNS pathology may deserve further investigation. As such, in addition to the development of optimal anti-viral drug delivery systems, more understanding of the indirect mechanisms responsible for HIV-1-associated dementia is essential. Viral and cellular proteins with neurotoxic properties may serve as early indicators of CNS disease and therapeutic efficacy. This notion is particularly important since early HIV-1-induced cognitive motor impairment may be associated with metabolic changes rather than CNS structural alterations. Furthermore, it is during this stage of the disease when alterations may be reversible. Attempts for the development of reliable, sensitive, and specific surrogate markers reflective of CNS disease derived from a peripheral sample was deemed valuable for designing therapeutic interventions.

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