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Clinical Science Workshop 3

Free session

Chairpersons: P. Portegies (Amsterdam, NL)
I. Grant (La Jolla, USA)

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Pro-glutathione compounds as alternative therapeutical strategy in neuroaids

P. Mialocq,[1] J. Oiry,[3] A.C. Rimaniol,[1] J.Y. Puy,[3] G. Gras,[1] J.L. Imbach,[3] N. Dereuddre-Bosquet,[2] D. Dormont,[1] P. Clayette[2]
1. Service de Neurovirologie, CEA (Fontenay aux Roses, FR)
2. SPI-BIO, c/o Service de Neurovirologie, CEA (Fontenay aux Roses, FR)
3. Université Montpellier II (Montpellier, FR)

Oxidative stress seems to play a major role in HIV pathogenesis. It increases HIV replication through the activation of NF-kappaB and is involved in neuroAIDS, particularly through increased apoptotic phenomenon. Glutathione (GSH) is the major intracellular antioxidant and its deficiency has been correlated with HIV replication and decreased survival of HIV-infected patients. In order to counteract these deleterious processes and to potentate the efficacy of antiretroviral molecules in the central nervous system, new pro-GSH molecules have been synthesized and their anti-oxidant and anti-HIV activities were evaluated *in vitro*. I-152, a pro-drug of N-acetylcysteine (NAC) and ß-mercaptoethylamine (MEA) has shown better antioxidant and direct antiviral properties as compared with these reference molecules. I-152 increases GSH level in several cell types such as human lymphocytes, monocyte-derived and tissular macrophages, in astrocytes (also involved in free radical detoxification and neuroprotection), as well as murine cortical neurons, particularly susceptible to oxidative stress-induced apoptosis). In pathophysiological conditions inducing a GSH deficiency i.e. HIV infection of MDM, I-152 restores the intracellular GSH level. Moreover, the antioxidant activity of I-152 is associated with anti-inflammatory effects i.e. decreased TNF-alpha synthesis in macrophages and neuroprotective effects in H_2O_2- or buthionine sulfoximine (BSO)-exposed neuronal cultures. At last, antiretroviral effects of NRTI, NNRTI and protease inhibitors is increased by co-treatment with I-152 confirming that pro-GSH molecules e.g. I-152 may be alternative therapeutical strategies in NeuroAIDS.

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Detection of JC virus DNA sequences and cellular localization of viral products T-antigen and agnoprotein in oligodendrogliomas

L. Del Valle,[1] S. Enam,[1] C. Lara,[1] C. Ortiz-Hidalgo,[2] C.D. Katsetos,[3] K. Khalili[1]
1. Temple University (Philadelphia, USA)
2. American British Cowdray Hospital (Mexico City, MEX)
3. St. Christopher's Hospital Children (Philadelphia, USA)

Productive infection of the human neurotropic polyomavirus, JCV in oligodendrocytes leads to the development of progressive multifocal leukoencephalopathy, a fatal demyelinating disorder of the central nervous system, histologically characterized by extensive plaques of myelin loss, intranuclear inclusion bodies in oligodendrocytes and the bizarre reactive astrocytes. Accounting for 4.2% of all primary brain tumors, oligodendrogliomas are slow growing neoplasms of the cortex. A significant percentage of oligodendrogliomas exhibit combined loss of chromosomes 1p and 19q, which clinically is considered to be a predictor of a favorable response to chemotheraphy and a better prognosis. However, the etiology of oligodendrogliomas remains presently unknown.

Recent studies from several laboratories point to the association of polyomaviruses, including JCV, with a variety of human brain tumors. In addition to its role in viral infection, JCV T-antigen has the ability to transform cells *in vitro* and to induce tumors in experimental animals in the absence of viral DNA replication and late gene expression.

The goal of this study was to examine the presence of JCV DNA sequences and viral antigens in a series of surgically excised human oligodendrogliomas. Gene amplification has revealed the presence of JCV DNA sequences corresponding to the N-terminal of T-antigen in 15 of 20 samples. DNA sequences corresponding to late regions, which are responsible for production of the capsid protein, VP1, were detected in 14 of 20 samples. Sequencing of the viral control region determined the presence of JCV Mad-4 or JCVCY in these tumors. By immunohistochemistry, T-antigen expression was detected in the nuclei of tumor cells from 10 samples that also contained corresponding DNA sequences by polymerase chain reaction. Eleven out of 20 tumors exhibited immunoreactivity for the late auxiliary gene product, agnoprotein. None of the samples showed immunoreactivity for the capsid proteins, ruling out productive infection of tumor cells by JCV.

Collectively, these observations provide new evidence in support of the association of the oncogenic human neurotropic, JCV, and oligodenrogliomas.

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Immunophilins and neurotrophin receptor response to neuronal degeneration in HIV encephalitis

C. Achim
University Pittsburgh School Medicine (Pittsburgh, USA)

Proposed mechanisms of disease in HIV infection of the brain are most often associated with glial and macrophage activation leading to neuronal death. We have previously shown that an alternate mechanism, more compatible with the chronic aspect of HIV encephalitis (HIVE), is the progressive loss of neuronal functions due associated with abnormal distribution of derived neurotrophic factor (BDNF) and its receptors trkB. More recently, we have described another marker of disease, the neuronal immunopohilin FKBP12 that can interact with HIV proteins gag and gp120.

Our preliminary studies showed that FKBP12 is expressed in the normal human brain, in basal ganglia, predominantly in neurons and occasionally in glia. Its levels are elevated in the substantia nigra, hippocampus and deep gray matter of patients with Parkinson's, Alzheimer's disease and dementia with Lewy bodies. We have now evidence that the truncated isoform of trkB is abundant in the post-natal brain where it may mediate critical synaptic functions. The current study analyzes alterations in FKBP levels in the basal ganglia and cortex of patients with HIVE and control subjects. The expression and distribution of FKBP12 are compared to trkB changes and other markers of neuronal degeneration.

The results of our studies show that expression of FKBP12 is significantly increased in areas of pathology in HVE characterized by presence of virus, glial activation, neuronal degeneration and disruption of BDNF and receptor distribution. The significance of the altered FKBP12 and truncated trkB expression in patients with HIVE is still to be determined. The increased levels might be linked to abnormal protein folding and axonal transport and also explain the selective vulnerability of the basal ganglia to HIV infection. Altered expression of FKBP12, a growth-associated protein, in brain regions affected by the disease process might also reflect a compensatory regenerative phenomenon. Finally, the dysfunction and abnormal distribution of the truncated trkB may indicate a deficient transport of BDNF and other chaperone molecules involved in normal synaptic functions.

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Virologic and neuropsychologic predictors of driving ability in HIV infection

T.D. Marcotte, R.D. Coleman, R.K. Heaton, M. Rivera-Mindt, J.A. McCutchan, S. Letendre, R.J. Ellis, E. Roberts, I. Grant
University of California-San Diego (San Diego, USA)

Objective: To determine the best laboratory-based predictors of impaired driving abilities in HIV-infected individuals.

Methods: 135 HIV-seropositive subjects underwent a detailed neuropsychological (NP) evaluation and laboratory determinations of CD4 lymphocyte counts in blood and HIV RNA levels in plasma and CSF. All subjects also completed a 15-minute PC-based driving simulation that required accident avoidance as well as performance of more routine tasks such as passing cars and responding to roadway signage. Based upon the number of simulator accidents occurring in a larger cohort of cognitively normal HIV+ subjects, subjects were classified as to whether they passed or failed the driving simulation.

Results: Thirty-eight percent of the subjects failed the simulation. Failing and passing subjects did not differ in age, gender, ethnicity, or educational level. The two groups were also similar in disease status (approximately 60% had an AIDS diagnosis), level of immunosuppression (CD4 counts of approximately 300), and plasma HIV RNA levels (approximately 3.5 log c/mL). However, subjects who failed the simulation had higher HIV RNA levels in CSF than those who passed (mean 2.1 vs. 1.6 log c/mL; $p = .05$) and a significantly higher rate of cognitive impairment (67% vs. 24%; $p < .0001$). In a regression model, HIV RNA levels (plasma and CSF) and cognitive performance explained 15% of the variance in simulator success ($p < .0001$); cognitive status was the only significant predictor, with a trend for CSF HIV RNA levels ($p = .14$). In another model, NP status ($p < .0001$) and CSF viral levels ($p = .04$) accounted for 16% of the variance in the total number of simulator accidents.

Conclusion: Stage of HIV disease does not differentiate among those who may or may not have impaired driving abilities. Higher CSF HIV RNA levels are associated with worse performance on a driving simulator, yet neuropsychological status remains the best indicator of potential driving difficulties.