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Workshop

Bornavirus

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Neuropsychiatric-like disorders in transgenic mice expressing Borna disease virus phosphoprotein in the CNS

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Neurobehavioral disorder is a serious consequence of a number of viral infections in the central nervous system (CNS). A line of evidence has demonstrated that viral infections are associated with disturbances in neural functions that may be caused by alteration of the brain homeostasis. Here, we examined the role of viral persistent infection in neuropsychiatric disorders by generating a transgenic mouse expressing the 24 kDa-phosphoprotein (p24) of Borna disease virus (BDV) in the CNS.

Under the control of the enhancer-promoter region of the glial fibrillary acidic protein, we generated transgenic mice expressing BDV-p24 in the CNS. We demonstrated that BDV p24 interferes with the function of a multi-functional protein, HMGB1, in infected cells, suggesting some neurotropic effects of the p24 in infected CNSs. Glial expression of the transgene revealed a gradual deposit of the p24 in the CNS, especially at the neuropil in the hippocampus, without astrocytosis and neuronal degeneration. Behavioral analyses of the transgenic mice showed enhanced intermale aggressiveness and impairment of cognitive abilities. Furthermore, the transgenic mice showed progressive and marked decrease of synaptic density, which led to significant reduction in the brain-derived neurotropic factor. Thus, glial deposition or accumulation of BDV p24 may induce deleterious effects on the synaptic formation in the CNS, which may lead to neurobehavioral alterations.

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Selective virus resistance conferred by expression of Borna disease virus nucleocapsid components

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Persistent viral infections can render host cells resistant to superinfection with the same or closely-related viruses. We observed that Vero cells persistently infected with Borna disease virus (BDV) were resistant to infection with a distinguishable second strain of BDV. We further found that persistently infected, immunologically tolerant rats that were infected with BDV as newborns were highly resistant to superinfection when challenged 8 or more days later. Expression of cDNAs coding for either the phosphoprotein P or the nucleoprotein N of BDV but not irrelevant control proteins rendered human UTA6 cells resistant to subsequent challenge with BDV but not several other RNA viruses. Cells containing high levels of an untranslatable transcript of the BDV-N gene remained virus-susceptible, indicating that viral proteins rather than viral RNAs mediate resistance. Expression of cDNAs for either N or P in cells that were chronically infected with BDV resulted in strikingly altered intracellular distribution of the transgene products. While transgenic expression of N had no deleterious effect on the persisting virus in UTA6 cells, P was also able to block BDV under these conditions. BDV did not replicate in neurons of transgenic mice expressing N under the control of a neuron-specific promoter, indicating that novel therapeutic concepts based on non-balanced expression of viral nucleocapsid components might be feasible. We hypothesize that correct stoichiometry of viral nucleocapsid components is essential for BDV polymerase function and that the polymerase of incoming viral particles is particularly sensitive.

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The host-virus interaction in neonatal Borna disease virus infection: the pathogenic events mediating differential neurodevelopmental damage

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Neonatal Borna disease virus (BDV) infection in the rat produces a constellation of neurobehavioral abnormalities similar to human neurodevelopmental disorders. We evaluated neonatal BDV infection-associated neurodevelopmental damage in two inbred rat strains, Fisher344 and Lewis, characterized by differential responsivity to environmental insults. Despite similar viral replication and weight gain inhibition, neonatal BDV infection produced more extensive shrinkage of the neocortex in Fisher344 rats compared to Lewis rats at day 30 and 120 post infection (p.i.), while degeneration of the dentate gyrus of the hippocampus and hypoplasia of the cerebellum were similar in the two rat strains at day 30 and 120 p.i. Greater virus-associated up-regulation of serotonin (5-HT) tissue contents and densities of postsynaptic 5-HT1a and 5-HT2a receptors were observed in Fisher344 rats compared to Lewis rats at day 14 p.i., followed by BDV-associated decrease in receptor density in both rat strains. BDV-associated alterations in dopamine turnover and the density of dopamine receptors were predominantly found in Fisher344. Virus-associated monoamine disturbances might explain strain-related impairments of prepulse inhibition of the acoustic startle and hyper-reactivity to novelty as well as differential sensitivity to treatments with monoamine compounds. The present data indicate the utility of neonatal BDV infection for the study of the pathogenic processes of virus-induced neurobehavioral disease in hosts with differential susceptibility to environmental insults. Supported by MH-48948.

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Degenerative lesions in the brain of newborn-thymectomized rats infected as adults with Borna disease virus

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The neurotrophic negative-strand RNA Borna Disease Virus (BDV) infects different species and causes clinical symptoms ranging from subtle disturbances of motility and sensorium to dementia. Whilst in some of the natural and experimental hosts the expression of BDV-specific antigens causes severe polioencephalitis, other recipients show only minor clinical and neuropathological changes. The reason for the varying intra- and interspecies courses of Borna disease (BD) are unknown. Other than BDV-infected normal adult Lewis rats (BDV-AD), newborn-thymektomized rats infected as adults (BDV-NBTx) fail to develop typical BD, i.e. lymphocytic polioencephalitis and severe neurological disorder. If any, NBTx show only transient and/or slight behavioural abnormalities and neurological symptoms e.g. abnormal gait and ataxia. There is no immunomorphological evidence of T cell infiltration in the brain, and no upregulation of CD4, CD8, MHC I, IFN-beta and g, TNF-alphy and beta, and MIF can be detected by RNAase protection analysis. However, immunocytochemistry reveals reduced tyrosine hydroxylase (TH) labeling in frontal and parietal cortex and in the hippocampus by day 30 to 40, and neuronal degeneration by three to six months postinfection. These results indicate that the presence of immunopathological reactions in the brain is not the only prerequisite to neuronal damage in BD.

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Testing the mild encephalitis hypothesis in schizophrenia and affective psychosis

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Objective: Mild encephalitis (ME), assumed to be mainly characterized by humoral inflammatory upregulation possibly from virus-induced immune activation, may underlie and basically explain a share of so-called major psychoses. This hypothesis was tested by investigating in parallel various immune-inflammatory markers in CSF- and blood-compartment of psychotic patients.

Methods: In 40 patients (20 Borna disease virus seropositive, 20 Borna disease virus seronegative) with schizophrenic (20) or affective psychoses (20) the following parameters were investigated in parallel in blood and CSF: BDV antibodies (by IFA and immunoblot), Borna disease virus (by PCR) [S.H.]. T cell repertoire (V beta chain) in CSF and blood lymphocytes [E.O.]. QYNAD or QYNAD like peptides known from autoimmune inflammatory neurological disorders [H.B. and coworkers]. Tryptophan-kynurenine-neopterin pathway as indicator of immune activation [D.F.]. Conventional CSF inflammatory markers: oligoclonal bands, protein contents, especially IgG and IgM, compared to respective values in blood [H.T.].

Results: In about 50% of psychotic patients yet investigated (n = 18), including both BDV seropositive and BDV seronegative patients, pathological immune-inflammatory markers were found in CSF but not in blood. These were as follows: oligoclonal expansion of T cell repertoire; oligoclonal bands and/or IgG/IgM protein abnormalities. QYNAD or a QYNAD like molecule. Tryptophan-Kynurenine-Neopterin parameters indicated immune activation in about 1/3 of patients.

Conclusion: When tested with sensitive methods, especially analysis of T cell repertoire of CSF lymphocytes, about 50% of patients suffering from major psychoses of schizophrenic or affective type show an immune-inflammatory activation within CSF spaces. This may indeed be causally related to psychoses and supports ME hypothesis, because immune-inflammatory activation was restricted to CSF spaces and therefore cannot be explained by a general infection or immune activation. Whether in some patients immune-inflammatory activation was related to previous Borna disease virus infection however remains to be determined.