

Persistent virus infections of the CNS tissue may lead to functional and structural alterations of the host cell accompanied by psychological and neurological changes. In coronavirus infection of rats a persistent infection is the basis for the development of a sub-acute demyelinating encephalomyelitis (SDE). Animals surviving this infection may develop a relapsing course accompanied by old and fresh demyelinating lesions. The age of the animal, the time of infection, the response of the immune system, the genetic background of the host as well as the properties of the virus mutant used for infection determine the outcome and development of the CNS disease process. Of particular interest is the finding that spleen cells from diseased rats are sensitized against myelin basic protein (MBP) and adoptive transfer of such cells causes CNS changes similar to experimental allergic encephalomyelitis (EAE). In addition, rats which develop a remission of SDE are resistant to subsequent induction of EAE when challenged with MBP. Analysis of cerebrospinal fluid from rats at different stages of the disease reveal intrathecal IgG synthesis which are in part specific for corona virus antigen. These data indicate that in the course of coronavirus infection in rats an autoimmune reaction against brain antigen develops which may be of pathogenetic importance. This phenomenon may also play a role in the development of other CNS disorders.

Abstract 36. In vivo and in vitro models of demyelinating disease: factors influencing the disease process caused by coronavirus infection of the rat
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The coronaviruses, ubiquitous in mammals, including man, manifest serotype-related predilection for different tissues. The murine viserotropic strain is MHV3 and neurotropic in JHMV. JHMV when inoculated into neonatal rats, can cause either a rapidly fatal acute encephalomyelitis or, after longer incubation periods, a paralytic disease. High anti-JHMV IgG ratios of CSF/serum, indicative of local antibody production in the CNS, were noted only where disease was demonstrable, suggesting that local antibody production accompanied the infection but did not prevent the neurological disease. Among animals in which neurologic symptoms had not become manifest, only those with elevated CSF/serum ratios were found to have histological CNS lesions. Immunofluorescent microscopy indicated that viral antigens were present in both glia and neurons. Antigen-positive cells were frequently present in histologically normal CNS tissue, while regions of necrosis were antigen-negative. Testing for the presence of viral RNA with JHMV cDNA probes revealed that the virus was rapidly disseminated throughout the CNS, presumably establishing centers of infection prior to the development of recognizable tissue damage. Viral RNA was also detected in the CNS following recovery from paralysis and as late as 5 months post-infection, where no disease occurred. These findings indicate that, although infection by JHM virus can spread rapidly throughout the CNS, formation of lesions during chronic disease is a slower process. The current data and previous observations suggest that in rats JHMV can remain in a latent state for periods of at least several months, without apparent neurologic disease, despite the absence of any known provirus phase in the replicative strategy of coronaviruses.

Concerning the serotype specificity for explanted cells from the CNS of newborn, inbred, Wistar-Furth rats, an unambiguous tropism of MHV3 for astrocytes and JHMV for oligodendrocytes could be demonstrated. With the latter cell-virus interaction, relatively small differences in spatial density of oligodendrocytes influence profoundly the duration of persistence and virus yield.

The *in vitro* temporal programme of oligodendrocyte differentiation, monitored by induction of a myelin related enzyme, 2':3'-cyclic nucleotide-3'-phosphohydrolase, corresponds to that occurring *in vivo* and is coincident with the onset of insusceptibility to disease caused by JHMV. On the basis of these data it is concluded that *in-vitro* interaction of JHMV with oligodendrocytes reflects accurately the *in-vivo* host control over the tropism and expression of this virus, thereby effecting the progressive, demyelinative disease process.