EFFECT OF CYCLOSPORIN A ON MHV3-INDUCED CHRONIC CNS INFECTION IN MICE

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Intraperitoneal injection of MHV3 into adult C₃H mice results either in early death due to hepatitis or in the development of a chronic disease with neurologic manifestations and virus persistence in surviving animals. The chronic neurologic disease which is described in another report in this volume, leads to meningitis, ependymitis, encephalitis and hydrocephalus followed by a chronic thrombotic vasculitis. In view of the potential therapeutic interest of Cyclosporin A (CsA), we decided to test its effects on the CNS lesions induced by MHV3.

One hundred and four 10 weeks old C₃H mice were injected i.p. with 10^2 pfu of MHV3. Thirty-five of these mice received daily 50 mg/kg of CsA subcutaneously and the 64 other infected mice were kept as untreated control animals (some of them being treated later by CsA). CsA titers in whole blood (measured by HPLC technique), tested 24 hours post inoculation at different times of the treatment course, was between 1300 and 3500 ng/ml.

1. Effect of CsA treatment on the acute MHV3 induced disease in C₃H mice

The percentage of acute death was slightly higher in CsA treated mice (32 % of death) compared to control infected mice (16 % of death). Similarly, viral titers (4th day post-infection) in liver and brain of CsA treated mice (liver 2.9×10^5 pfu/g ; brain 5.5×10^5 pfu/g) were higher than in the same organs of control infected mice (liver 3.6×10^4 pfu/g, brain 6.4×10^2 pfu/g). Interferon titers (24 hours post-infection) were similar in CsA-treated and control infected mice.

2. Effect of CsA treatment on the chronic CNS disease

CsA treated and control infected mice were followed for 12 weeks post-infection. CsA treatment did not modify the percentage of death during the chronic disease except after the 8th week of treatment when the percentage of death increased in the group of CsA-treated infected mice but also in a control group of similarly CsA-treated uninfected animals. Viral titers in the brain and liver of chronically infected mice were similar in CsA-treated and control infected mice, as were anti-MHV3 antibody titers (Elisa technical). Neuropathological lesions

(meningitis, ependymitis/hydrocephalus and vasculitis) were markedly reduced in the brain of CsA-treated mice when compared to control mice.

When CsA treatment was begun 15 days after MHV3 inoculation and subsequently injected daily up to the end of the experiment, results were close to those observed in animals whose CsA treatment began at the same time as viral infection. On the other hand, in group of 7 mice, CsA treatment was started 35 days p.i. and maintained up to the 12th week p.i., the percentage of animals expressing neuropathological lesions was similar to that obtained in untreated infected mice but less intensively.

In conclusion, CsA treatment appears to be effective on the neuropathological consequences of MHV3 infection suggesting that meningitis, ependymitis/hydrocephalus and vasculitis may depend not only on the direct effect of the virus on one of its target cells but also on the immune response against virus-infected cells.