RESISTANCE TO MURINE HEPATITIS VIRUS STRAIN 3 (MHV-3) INFECTION IN A/J MICE IS NOT AFFECTED BY CYCLOSPORIN A (CSA)

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Infection with mouse hepatitis virus strain 3 (MHV-3), causes a strain dependent spectrum of liver disease in inbred mice[1]. Mice of the A strain (A/J) are fully resistant to the virus and develop no evidence of liver disease. This resistance cannot be explained by restriction of viral replication, as high titers of infectious virus can be recovered from livers of these and resistant mice. Resistance to MHV-3 is dependent upon suitable numbers of both T cells and macrophages[2] and immunosuppression with methylprednisolone, antilymphocyte globulin and cyclophosphamide results in conversion of resistance to susceptibility[3].

The present studies were designed to i) examine the effects of the selective immunosuppressant CsA on the course of MHV-3 infection in the fully resistant A/J strain, and ii) to confirm previous reports regarding the effects of immunosuppression with cyclophosamide and methylprednisolone.

Adult A/J male mice (Jackson Laboratories, Bar Harbor, Me) were infected with 10^6 plaque forming units (PFU) of MHV-3 intraperitoneally (i.p.). They were treated with either CsA (Sandoz, Basle, Switz.) 50 mg/kg subcutaneously once daily Cyclophosphamide (Cy) (Procytox, Pointer Laboratories, Montreal, PQ) 75 mg/kg i.p. once daily, or methylprednisolone (MP) sodium succinate (Solu-Medrol, Upjohn Co. Don Mills, Ontario, Canada) 500 mg/kg i.p. once daily. Immunosuppression was initiated in all animals 72 hours prior to infection with MHV-3 and continued throughout the course of the study.

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RESULTS AND DISCUSSION

CsA, Cy, or MP alone had no deleterious effects on control animals when used at the aforementioned dosages. Animals infected with 10^6 PFU of MHV-3 were fully resistant to the virus and showed no morbidity or mortality and no histologic evidence of hepatitis (Table 1, Figure 1A). Animals which were treated with MP or Cy and subsequently infected with MHV-3 unequivocally developed fulminant viral hepatitis as evidenced by histology and biochemistry and died within 7 days of infection. (Table 1,Figure 1B,C).

In mice treated with CsA, serum levels were determined at 12 hours (4830±650 ng/ml) and 24 hours (628±315 ng/ml) following administration. No biochemical or histologic evidence of hepatitis could be detected in animals which were treated with CsA and subsequently infected with MHV-3.(Figure 1D, Table 1). The antibody response to MHV-3 (IgM and IgG) which was observed in the treated (CsA) and infected (MHV-3) animals was similar to that of animals infected with MHV-3 alone. High titers of infectious virus were recovered from the livers of MHV-3 infected animals, and the virus was cleared from their livers by day 10. Animals pretreated with CsA and infected with MHV-3, although having similar titers of virus, revealed a slight delay in clearance of the virus from their livers (Day 14) (Table 1).

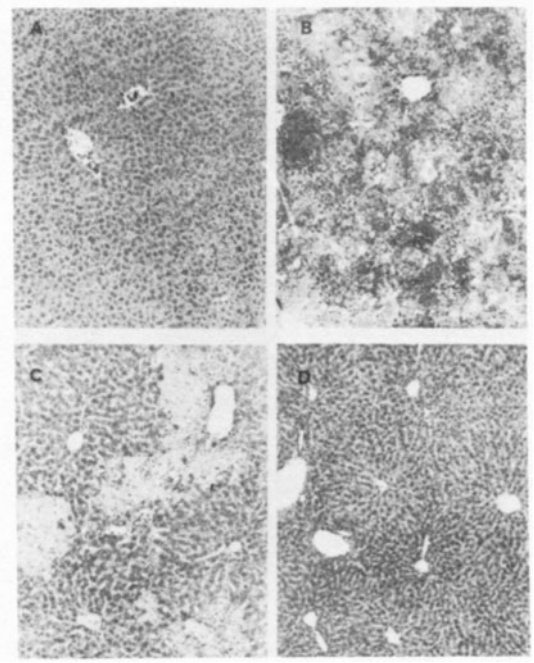

Figure 1. Liver Histology (H +E) in A/J mice. A) Normal histology in mice infected with MHV-3. B) + C) Cy and MP pretreatment respectively followed by MHV-3 infection showing fulminant hepatitis and D) CsA pretreatment followed by MHV-3 infection with no evidence of hepatitis.

TABLE 1

EFFECTS OF IMMUNOSUPPRESSION ON THE COURSE OF MHV-3 INFECTION

GROUP	MORTALITY (# Died/Total Studied)	ALT (IU/Liter)	Peak VIRAL TITERS (PFU/gm Liver)	Peak ANTIBODY (cpm)
Control	0/10	50±10	-	0
MHV-3	0/10	45±7	10^9	1,450±192
CsA + MHV-3	0/10	60±30	10^8	1,662±416
Cy + MHV-3	10/10	1,250±300	-	-
MP + MHV-3	10/10	1,500±450	-	-

Mortality was determined by day 10. Peak antibody levels were observed by day 14 p.i.

The data presented here demonstrate that CsA, at a dosage which results in serum levels far in excess of therapeutic values fails to alter innate resistance of A/J animals, whereas suppression with non-selective agents (OY, MP) induces susceptibility.

REFERENCES

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