PROSTAGLANDIN E2 (PGE2) ALTERS THE PATHOGENESIS OF MHV-3 INFECTION IN SUSCEPTIBLE BALB/cJ MICE

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Murine hepatitis virus type 3 (MHV-3) produces a strain dependent pattern of disease in inbred strains of mice. Balb/cJ mice develop fulminant hepatitis following MHV-3 infection.[1]. Direct viral cytopathic effects do not account for the full spectrum of the disease and it appears that host immune factors are important in the pathogenesis of the disease. We have previously demonstrated that the induction of a specific macrophage protease (procoagulant activity (PCA)) correlates directly with susceptibility to disease and that it is responsible for disturbances in the microcirculation characterized by microthrombi, vasculitis, thrombosis and cellular necrosis.[2]. Little attention has been devoted to the effects of prostaglandins on viral infections. These studies were undertaken to examine the effect of 16, 16 dimethyl prostaglandin E2 on an experimental animal model of viral hepatitis.

Fully susceptible Balb/cJ mice infected with MHV-3 (100 LD_{50}) developed histologic and biochemical evidence of fulminant hepatitis as evidenced by massive hepatic necrosis and a markedly elevated serum ALT (1,402±619 IU/Liter). In contrast, animals treated with PGE2, either prior to or following infection (2 ug/kg,i.p.) demonstrated little or no biochemical and histologic evidence of disease (ALT: 63±40 IU/Liter) (Table 1). High titers of infectious virus were recovered from the livers of both PGE2 treated and non-treated animals throughout the course of the infection.

Table 1. THE EFFECT OF PGE2 ON MHV-3 INFECTION

Group	Serum ALT	Morphometry (% necrosis)	Viral Titers (Log_{10} gm liver)	PCA (mU/10^6 macrophages)
PGE2	20±15	0	0	46±20
MHV-3	1402±619	93	$2x10^8 \pm 1x10^7$	615±262
MHV-3 + PGE2	63±40	24	$6x10^8 \pm 1x10^8$	96±70

These represent peak values obtained 96 hours post infection.

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In addition,splenic macrophages recovered from Balb/cJ mice which were infected with MHV-3 demonstrated a marked augmentation in PCA from a basal 10±5 mu/10^6 macrophages to a maximum of 615±262 mu/10^6 macrophages whereas no increase in macrophage PCA was detected in infected animals which had been treated with PGE2. In the MHV-3 infected hepatocytes cultures,cytopathic effect was observed by 18 hours as demonstrated by cell fusion. By 48 hours cell lysis occurred with the destruction of the hepatocyte monolayer.(Figure 1). In contrast, in the infected monolayers treated with PGE2 little or no cytopathic effect was evident.

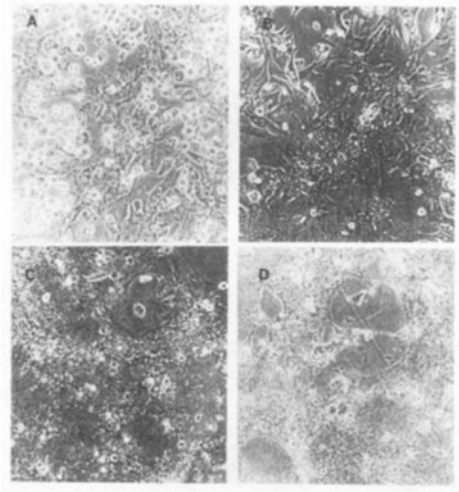

Figure 1. In Vitro Hepatocyte Cytoprotection by PGE_2. Little or no cytopathic effect was observed in hepatocytes infected with MHV-3 (m.o.i. 1.0) in the presence of 10^{-4} M PGE_2 at (A) 24 hours and (B) 48 hours whereas syncitial formation occured at (C) 24 hours and cell lysis at 48 hours (D) in MHV-3 infected but PGE_2 untreated cells.

The present studies demonstrate a cytoprotective role for PGE2 both in-vivo and in-vitro following MHV-3 infection. It is evident from our results that PGE2 does not affect either replication or infectivity of the virus. This is demonstrated by the recovery of similar titers from both PGE2 treated or untreated infected animals, as well as by the ability of the extracted virus from both groups to produce comparable mortality in fully susceptible Balb/cJ mice. Thus, although the virus is present and retains its infectivity in the livers of PGE2 treated animals, the cytopathic effect which it is usually associated with is abrogated. Although, the exact mechanism of this cytoprotection is not clear, the present results in-vitro suggest that PGE2 acts at least in part at the hepatocyte level. In addition, the failure of induction of PCA in PGE2 treated animals suggests a role for the immune system in the pathogenesis of the disease.

REFERENCES

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