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Fulminant Hepatitis

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Introduction

Fulminant hepatitis (FH) as a consequence of hepatitis B virus infection is a rapidly fatal disease occurring within 4–6 weeks of onset of jaundice leading to acute liver insufficiency, complicated by hepatic encephalopathy (HE) [9, 100]. If the HE occurs in less than 2 weeks after the onset of jaundice, the disease is termed acute FH, whereas subacute FH is defined as acute liver failure complicated by HE 2 weeks to 3 months after the onset of jaundice [9]. The incidence of FH is thought to be 0.1%–1.0% of all cases of acute hepatitis [7, 82, 83] and the mortality varies with the severity of HE, from 60% in stage II to over 90% in stage IV encephalopathy [4, 38, 60, 102]. Death can be attributed to a number of complications of FH [17, 99], but in 20% of cases, the cause of death is unknown. At autopsy, the liver shows massive hepatic necrosis with collapse and minimal evidence of hepatic regeneration [15, 61]. At the time of presentation viral antigens (HBV surface and core antigens; HBsAg, HBcAg) and the viral genome (HBV-DNA) usually are not found in liver tissue [15, 16]. No satisfactory medical treatment exists for FH. Management to date consists of supportive measures including repletion of plasma coagulation factors, glucose infusion, treatment of sepsis and correction of fluid and electrolyte imbalances [6]. No significant benefit of corticosteroids was shown in this setting [33, 39, 85] and in a recent randomized controlled trial, charcoal hemoperfusion was also shown to be of no benefit [3, 78]. Liver transplantation has been proposed for patients with FH; however, the survival in the most ill patients (stages III and IV hepatic encephalopathy) remains only 30%–40%, suggesting that if transplantation is to be offered, it should be considered earlier [18, 81, 91].

The pathogenesis of the disease is unknown but appears to involve viral factors as well as host factors including age, sex and the immune status of the host [15,

Abbreviations: DIC disseminated intravascular coagulation; *dmPGE*$_2$ dimethyl prostaglandin E$_2$; *ELAM* endothelial-leukocyte adhesion molecule; *FH* fulminant hepatitis; *HBV* hepatitis B virus; *HBcAg* hepatitis B core antigen; *HBsAg* hepatitis B surface antigen; *HE* hepatic encephalopathy; *IFN* interferon; *MHC* major histocompatibility complex; *MHV* murine hepatitis virus; *PCA* procoagulant activity; *PG* prostaglandins; *TNF* tumor necrosis factor; *2-5 AS* oligoadenylate synthetase

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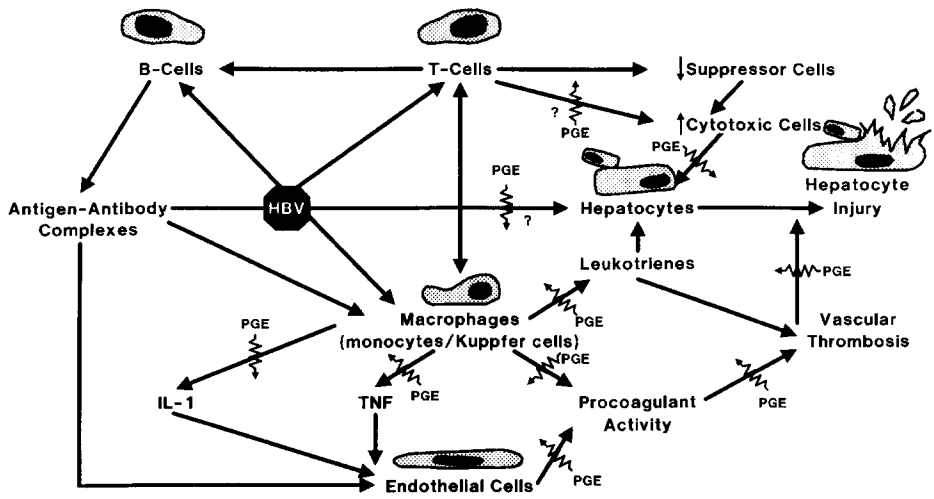

Fig. 1. Postulated mechanisms for hepatocyte injury in hepatitis B virus (*HBV*)-induced fulminant hepatitis. *PGE* Prostaglandin E; *IL*-1 interleukin-1; *TNF* tumour necrosis factor

16, 30]. There is considerable evidence to suggest that the hepatitis B virus (HBV) is not directly cytopathic for hepatocytes, but rather, hepatic injury may be a result of both humoral and cellular immune-mediated processes [51, 94–96]. Evidence exists in experimental models of FH and in man which suggests that following viral infection, the immune coagulation system is activated [53, 54]. This results in intravascular thrombosis and localized microcirculatory disturbances within the liver [68–70]. Agents which interfere with activation of the classical or immune coagulation systems have been shown to be beneficial in the setting of FH [68].

Based upon these observations, we have developed the following hypothesis for the pathogenesis of FH (Fig. 1). Viral infection results in cellular and/or humoral immune responses which are either directly injurious to the liver, or result in activation of the immune coagulation system with formation of sinusoidal microthrombi, platelet activation and hepatic necrosis. The failure of regulation of these pathways results in the clinical syndrome of FH. The remainder of this chapter will discuss the evidence which forms the basis for this hypothesis.

Pathogenesis

Humoral Immune Response to HBV

Vigorous immune responses to HBsAg have been reported in FH B infection [17, 36]. HBsAg was cleared from the serum significantly faster in patients with FH than in serum from patients with non-FH. Furthermore, in a significant proportion of the patients with FH, an antibody response to HBsAg (anti-HBsAg) was detectable at presentation [7, 98, 103]. Since little or no antibody to HBsAg is detected during acute viral hepatitis B infection it has been postulated that the presence of both antigen and antibody (immune complexes) in these patients (FH) may be

responsible for the severe liver disease that ensues [8, 76, 98, 103]. More recently it has been demonstrated that antibodies to the translation products of the PreS1 and PreS2 regions of the envelope gene of HBV occur early during the course of FH B and may participate in the severe hepatic injury and early clearance of virus, characteristic of this disease [44]. These results suggest that the enhanced humoral immune response with production of antibody may lead to an Arthus-like reaction in the sinusoids of the liver with ensuing ischemic necrosis [98].

Cellular Immune Response

It has been suggested that cellular immune mechanisms are responsible for hepatocellular injury in viral hepatitis [15, 16, 21, 22, 30, 41, 42, 45, 62, 63, 66, 80]. Elimination of virally infected hepatocytes is dependent upon the recognition of viral determinants in association with major histocompatibility complex (MHC) proteins (class I) on infected hepatocytes by cytotoxic T cells [21, 45, 51, 104]. More recent studies have suggested that natural killer (NK) cells play a role during the acute phase of the disease [31]. Autologous cytotoxicity studies suggest that the target antigens known to be expressed on the surface of infected hepatocytes are HBcAg and/or HBsAg [15, 16]. Using dual-color fluorescence analysis, an elevation in Leu-$2a^+15^-$ (cytotoxic) cells as well as a reduction of Leu-$2a^+15^+$ (suppressor) cells were found in the peripheral blood in patients with FH [41]. Serial studies showed an imbalance of these two Leu-2a subsets of cells in the acute phase of infection, but not in the recovery phase (Table 1). In an attempt to identify intrahepatic lymphocyte subpopulations in patients with FH, it was demonstrated that there was an increase in cytotoxic T cells in liver tissue and that these cells were in broad contact with the surface of hepatocytes. In contrast, T helper cells were scarce in liver tissue. These results suggest that there is a loss of suppressor T cells and an increased number of cytotoxic T cells in the livers of patients with acute FH [21, 22, 80].

Activation of the Immune Coagulation System in FH

About 50% of cases of FH are associated with a moderate to severe consumption coagulopathy, or disseminated intravascular coagulation (DIC) [17, 52, 67–69]. Histopathological studies in man have revealed severe and extensive hepatic cell necrosis as the most conspicuous and common abnormality seen in the liver. This morphologically resembles hepatic necrosis produced experimentally in the rabbit by a Schwartzman reaction using *Escherichia coli* endotoxin [67]. This has led

Table 1. T lymphocyte subpopulations in patients with fulminant hepatitis (FH)

T lymphocytes	Peripheral blood	Liver tissue
Suppressor	Decreased	Decreased
Cytotoxic	Increased	Increased
Helper	----	Decreased

----: Data not available

to the hypothesis that the acute, severe and extensive hepatic cell necrosis which is seen in these cases is probably the result of an anoxic state caused in most instances by intrahepatic circulatory disturbances [67–69]. Thrombi formation has been noted in and around the necrotic areas in a significant number of cases of FH in man [69]. Further experimental evidence to support a role for activation of the immune coagulation system was seen in a murine model of viral hepatitis (MHV-3) in which production of a macrophage serine protease [procoagulant activity (PCA)] precedes and is genetically linked to the evolution of FH [26]. Abrogation of production of PCA either by heparin and/or prostaglandins prevented FH, although it did not prolong survival [1, 68]. Macrophages stimulated with endotoxin can be induced to express monokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). These have been shown to be capable of initiating induction of procoagulants by endothelial cells [10, 13, 14, 23]. Activated endothelial cells also produce an adhesion molecule (endothelial-leukocyte adhesion molecule 1, ELAM-1) which promotes adhesion of lymphocytes to endothelial cells and produces vascular stasis [11, 12, 23]. The normal function of endothelium is to inhibit thrombosis [37], therefore nonstimulated endothelial cells have very little surface procoagulant activity and normally augment the anticoagulant function of activated protein C [32, 71–74]. However, following stimulation of endothelial cells, the balance is tipped in favor of thrombosis [23, 37]. The promotion of coagulation as a result of interaction of monocytes and endothelial cells may be beneficial in limiting the spread of the infectious agent and act as a natural defence mechanism. On the other hand, the same tendency to coagulation may lead to disseminated intravascular coagulation as has been seen in certain infections and malignancies and this may be detrimental to the host [52].

Interferon (IFN) and Fulminant Viral Hepatitis

IFN is not normally found in measurable quantities in serum but is detected in the acute phase of a number of viral infections [25, 50, 92]. The detection of IFN has not been noted consistently in acute hepatitis B, but indirect evidence such as increased expression of MHC class I antigens on hepatocyte membranes [25, 70, 87] and increased 2,5-oligoadenylate synthetase (2,5-AS) activity in peripheral blood mononuclear cells suggest that IFNs play an important role in the clearance of the virus [25, 49]. Adult HBV carriers have a decreased capacity for production of IFNs by mononuclear cells in response to appropriate in vitro stimulation [43]. The hepatocytes of these patients do, however, show augmented 2,5-AS activity in response to exogenous IFN-α [43]. It is not clear whether this apparent IFN deficiency is a primary phenomenon which predisposes the patients to chronic HBV infection or a secondary phenomenon related to chronic infection [88]. In a small series of patients with FH, IFN activity could not be detected in the serum [64]. In addition, infusion of IFN appeared to have no beneficial effect, with no increased survival [46]. In an experimental animal model of FH (MHV-3), although the exogenous infusion of IFN prolonged survival, there were no long-term survivors and all animals died of fulminant hepatic failure. Thus, although there may be an intrinsic defect in the IFN system in patients with FH, exogenous

IFN administration appears to confer no beneficial effects. Thus, the role of IFN in FH remains to be defined.

Prostaglandins in FH

Prostaglandins (PG) belong to a family of bioactive lipids derived from arachidonic acid via the cyclooxygenase pathway [47] (Fig. 2). Almost all of the cells of the body are able to produce PG, the most frequent type being PGE_2, a mediator of pain and edema in inflammation [47]. PGE_1 is much less abundant than PGE_2, but has similar biological effects. Both compounds are equally potent in causing fever, promoting pain and suppressing the synthesis of leukotriene B_4 by granulocytes [40]. PGE_1 induces the chemotactic response of neutrophils [40], and suppresses the effect of histamine and of other mediators of increased vascular permeability [34]. As with PGE_2, most of the PGE_1 effects may be explained by a stimulation of adenylate cyclase and the resulting elevated cyclic adenosine monophosphate (cAMP) levels [19, 20, 40]. In addition, PG have been demonstrated to inhibit IL-2 production [84], MHC class I and class II antigen expression [35, 59, 90, 93, 101], the induction of macrophage PCA by MHV [1] and cytotoxic T cell activity against autologous hepatocytes [77].

PG have been shown to have a beneficial effect in a variety of animal models of hepatic failure due to toxins (CCl_4, acetaminophen, galactosamine, alcohol, hypoxia, ischemia and immune mediation [4, 5, 24, 58, 65, 75, 77, 86]) (Table 2). Our group has shown hepatic cytoprotection by dimethyl PGE_2 ($dmPGE_2$) in fulminant murine viral hepatitis infection (MHV-3) [1]. Furthermore, preliminary evidence suggests that PG prevents the evolution and progression of brain edema

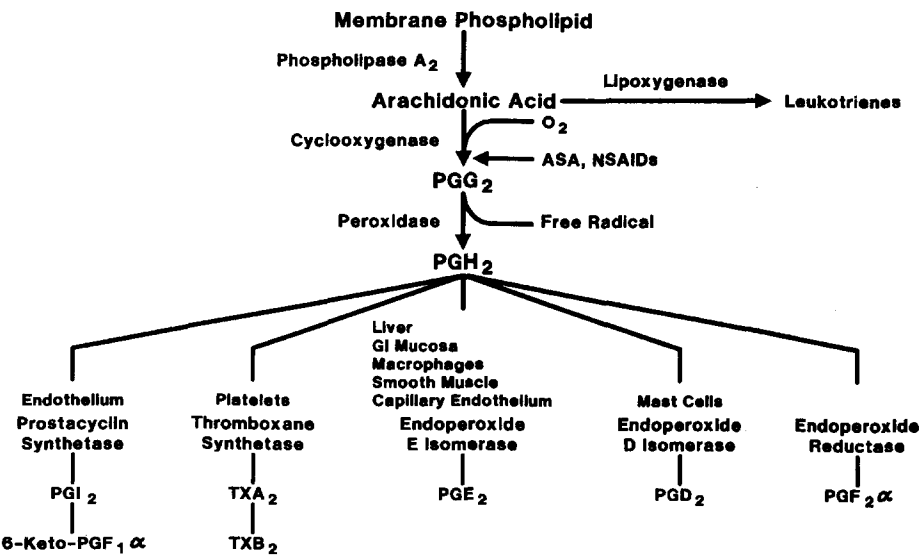

Fig. 2. Pathways for the production of prostaglandins (*PG*) from membrane phospholipids. *TX* Thromboxane; *ASA* acetylsalicylic acid; *NSAID* nonsteroidal anti-inflammatory drugs; *GI* gastrointestinal; PGI_2 prostacyclin

Table 2. Summary of hepatoprotective effects of prostaglandins (PG)

Type of injury	Damaging agent	Species	PG	Model
Fatty liver	Ethanol	Rat	PGE_1	In vivo
	Ethanol	Rat	dmPG	In vivo
	CCl_4	Rat	dmPG	In vivo
Hypoxia	$\downarrow Po_2$	Cat	PGI_2	Perfused liver
	Preservation at 4 °C without perfusion	Dog	PGI_2	Transplantation
Necrosis	Acetaminophen	Rat	dmPG	In vivo
	Galactosamine	Rat	dmPG	In vivo
	Galactosamine	Rabbit	PGE_1	In vivo
	Aflatoxin	Rat	dmPG	In vivo
	CCl_4	Rat	dmPG	In vivo
	Endotoxin	Mouse	PGE_1	In vivo
	Virus (MHV-3)	Mouse	dmPG	In vitro/In vivo

PGE_1 prostaglandin E_1; *dmPG* dimethyl PG; *PGI_2* prostacyclin; *MHV-3* murine hepatitis virus

in comatose FH rats [27–29]. Since brain edema is an important complication and cause of death in the setting of FH, prevention of brain edema by PGE_2 may explain the increased survival in animal models of FH [27–29].

Treatment

Medical

To date there is no known effective medical treatment for FH [6]. IFN therapy has proven to be of little value in this setting [46, 88]. The enthusiasm for charcoal hemoperfusion has declined since the recent report of a randomized controlled trial in which survival was not prolonged in patients with FH [79]. We have recently reported that infusions of PGE_1 results in increased patient survival in patients with FH [2, 89] (Table 3). Furthermore, in three patients with recurrent HBV infection following liver transplantation, infusion of PGE_1 resulted in clearance of HBsAg and HBcAg from the liver and amelioration of FH (manuscript in preparation). All three patients required oral PG to maintain this remission. Although the mechanism for the ameliorative effect is not known, PG may exert its beneficial effects by decreasing expression of class I and II antigens, inhibition of induction of monocyte/macrophage PCA and by preventing reinfection of hepatocytes (manuscript in preparation).

Liver Transplantation

Orthotopic liver transplantation has become the therapy of choice for chronic end-stage liver disease [18, 78, 81, 91]. More recently liver transplantation has been performed in patients with FH [18, 78, 81, 91]. Initial results suggest that this is an effective form of therapy in selected patients [18, 78, 81, 91]. However,

Table 3. Effect of PG in FH in man

Patient number	Etiological agent	Pre-PGE			Post-PGE		
		AST	BILI	PT	AST	BILI	PT
1	HBV	456	370	28	29	64	11
2	HBV	1420	214	38	34	80	12
3	HBV	2295	345	36	25	24	10
4	HBV[a]	750	161	28	66	22	12
5	HBV[a]	1100	451	17	45	238	11
6	HBV[a]	550	18	16	110	17	11

[a] Recurrent hepatitis B virus (HBV) infection following liver transplantation. Patients 4, 5 and 6 remain on oral PGE_2

AST aspartate transaminase (normal <20 U/l)
BILI bilirubin (normal <20 μmol/l)
PT prothrombin time (normal 11 s)

the most severely ill patients (stage III and IV hepatic encephalopathy) have only a 30%–40% survival following liver transplantation [18, 78, 81, 91]. Thus, transplantation for patients with FH, if to be considered, should be considered earlier rather than after the patients lapse into stage IV hepatic coma. Until controlled trials demonstrate the efficacy of PG or other agents, transplantation remains the treatment of choice for FH.

Discussion

The pathogenesis of FH B is not well understood. However, there is a body of evidence to suggest that HBV is not directly cytopathic to hepatocytes. Rather, the disease may be mediated by the humoral and cellular immune response to virally infected hepatocytes. At the time of the most severe injury there is usually an absence of both serological and virological markers of HBV infection, although a significant number of patients with FH have been shown to have anti-HBsAg, and aggregates of HBsAg and anti-HBsAg have been demonstrated in the sinusoids of the liver parenchyma. Surviving hepatocytes are devoid of hepatitis viral antigens and HBV-DNA [15, 16]. The predominance of cytotoxic T cells in the liver at the time of most severe injury would argue in favor of a cell-mediated immune response in the clearance of the virus.

The lesion of fulminant hepatic failure which is occasionally accompanied by fibrin thrombi deposition resembles the lesion of a disseminated Schwartzman reaction [67–69]. This observation suggests a participatory role for activation of the immune coagulation system in this disease process. It is known that both monocyte/macrophages and endothelial cells in response to endotoxin, viral antigens and immune complexes can produce proteases capable of initiating fibrin formation [23, 57]. This could result in microcirculatory thrombosis and hepatocyte hypoxia with progressive necrosis [67–69]. This sequence of events has been clearly elucidated in MHV infection [55, 56]. In vivo microscopic studies

of transilluminated livers in MHV-infected mice showed localized rounded areas with absent blood flow corresponding to the lesions seen in cast studies [55, 56]. Decreased velocity of red blood cells in adjacent sinusoids and complete stasis of blood flow was observed in some areas. Transmission electron microscopic studies of livers of infected mice have confirmed the obstruction of sinusoidal lumens by protruding lining cells, platelets and fibrin. These studies demonstrate that microvascular blockage may be an initial step leading to necrosis in a model of FH [55, 56].

It is known that eicosinoids and leukotrienes represent extremely potent mediators of inflammation and anaphylactic reactions [97]. While PG appear to be primarily vasodilatory, peptido-leukotrienes (LTC_4, LTD_4) are mainly vasoconstrictive [48, 97]. Treatment of animals with leukotrienes has been shown to result in FH, thus suggesting a possible role for these compounds in liver injury [97]. We, as well as others, have observed a beneficial effect of exogenous PG (PGE_1 and PGE_2) in the treatment of FH in an experimental animal model of FH and in man [1, 2]. PG of the E series are known to inhibit induction of monocyte/macrophage PCA [1] and activation of cytotoxic T cells [77]. Thus, the imbalance in production of prostanoids and leukotrienes during FH may account at least in part for the evolution of FH.

Conclusion

In conclusion, evidence exists that cellular and humoral immune-mediated processes result in hepatic necrosis in FH. Activation of the immune coagulation system appears to be an integral part of the inflammatory process resulting in fibrin thrombi which have been demonstrated in the liver, kidneys and lungs of patients with FH. A beneficial role of PG in the treatment of FH has been demonstrated, but controlled trials are required to firmly establish the efficacy of these agents. At present liver transplantation remains the treatment of choice in selected patients with FH. Further studies of the role of the immune system in the pathogenesis of this disease are required to devise more effective therapeutic strategies.

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