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Protective effects of prostaglandin E1 on hepatocytes

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INTRODUCTION

Numerous studies have demonstrated the protective action of prostaglandin E1 (PGE1) on experimental animal models of liver injury and on patients with fulminant viral hepatitis. It could act on PGE1 receptor of the diseased vessels to dilate them and increase portal venous flow, improve the microcirculation of the liver, clear the metabolites of the liver cells, and increase oxygen supply to the liver tissues. PGE1 could also accumulate at the inflammentory por tion, inhibit the release of lethal factors, stablize the membrane of liver cell s and lysosome, inhibit the active oxygen, and promote the proliferation of the liver cells. It is now used to treat fulminant hepatic failure.

PROTECTIVE ACTION OF PGE1 ON EXPERIMENTAL ANIMAL MODELS OF LIVER INJURY

The protective action of PGE1 has been shown on both experimental animal models of liver injury and patients with fulminant viral hepatitis. Beck *et al*[1] examined the effects of long-term PGE treatment on liver and stomach in cirrhotic rats. Cirrhosis was induced by bile duct ligation. Sham-operation was performed an controls. Half of the rats received a PGE1 anal ogue, misoprostol (PGE1) (10 μg orally, daily) on d 1 -d 29 postoperation, and the others received placebo only. Liver chemistry, portal pressures, and levels of prostaglandin E2, leukotriene B4, myeloperoxida se, and collagen in hepatic and gastric tissue of all rats on d 31 were determined. PGE1-treated cirrhotic rats had less hepatosplenomegaly, lower serum alanine aminotransferase levels, and portal pressures and higher arterial pressure than placebo-treated cirrhotic rats. Hepatic and gastric leukotriene B4, myeloperoxidase and collagen levels were significantly lower in the PGE1-treated compared with placebo-treated cirrhotic rats. Placebo-treated cirrhotic rats had greater spontaneous and ethanol-induced gastric damage and failed to show gastric hyperemic response to ethanol, whereas PGE1-pretreated rats did. PGE1 did not significantly affect sham-operated rats. Beck suggested that long-term PGE1 administration was cytoprotective for both the liver and ga stric mucosa in cirrhotic rats.

An animal model of hepatocytic necrosis was established by Gu[2] with injection of D-galactosamine into peritoneal cavity. Examination at regular intervals after injection of PGE showed that the level of increased serum TB, ALT and GST and the degree of histological changes in the liver were less marked in PGE-treated animals (n = 34) than those in PGE-untreated animals (n = 29), suggesting that PGE has definite protective effect on experimental hepatocytic necrosis.

The effects of PGE1.CD on dimethylnitrosamine (DMN)-induced acute liver damage with intravascular coagulation in rats were biochemically and histopathologicall y investigated by Suzuki[3]. PGE1.CD was administered i.v. 30 min before and 24 h after DMN-intoxication (pretreatment) and 30 min or 4 h to 24 h after DMN-intoxication (post-treatment). Pretreatment with P GE1.CD (0.2-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dose-dependently suppressed the decrease of platelet counts and the elevation of blood biochemica l parameters (PT, HPT, GOT, GPT, LDH, LAP, T-Bil) caused by DMN-intoxication. PGE1.CD (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or over) significant ly suppressed the DMN-induced histopathological changes (occurrence of hemorrhage and necrosis). Post-treatment with PGE1.CD (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) also suppressed the liver damage. Furthermore, pretr eatment with PGE1.CD (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) not only suppressed the disruption of hepatocytes, but also prevented the damages of sinu soidal endothelial cells and lysosomal membrane, and it reduced the increase of lipid peroxidation. PGE1.CD (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or over) significantly suppressed the decrease of hepatic tissue blood flow caused by DMN-intoxication. These results demonstrate that PGE1.CD has therapeutical efficacy against DMN-induced acute liver damage in rats, therefore, it will be clinically useful for the treatment of severe hepatitis such as fulminant hepati tis with intravascular coagulation in the sinusoid.

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PGE1 AND SEVERE HEPATITIS

The effect of PG on patients with fulminant and subfulminant viral hepatitis (FH F) was studied by Sinclair[4]. Seventeen patients presented with FHF sec ondary to hepatitis A (*n* = 3), hepatitis B (*n* = 6), and non-A, non-B (NANB) hepatitis (*n* = 8). Fourteen of the 17 patients had stage III or IV hepatic encephalopathy (HE). The mean aspartate transaminase (AST) was 1844U/L ±1246U/L, bilirubin 232 μmol/L ±135 μmol/L, prothrombin time (PT) 34s ±18s, partial th romboplastin time (PTT) 73s ±26s, and coagulation Factors V and VII 8% ± 4% and 9% ±5%, respectively. Intravenous PGE1 was initiated 24 h-48 h later a fter a rise in AST (2195U/L ±1810U/L), bilirubin (341 μmol/L ±148 μmol/L), PT (36s ±15s), and PTT (75s ±18s). Twelve of 17 responded rapidly with a decrease in AST from 1540U/L ± 833U/L to 188U/L ± 324U/L.Improvement in hepatic synthetic function was indicated by a decrease in PT from 27s ±7s to 12s ±1s and PTT from 61s ±10s to 31s ±2s, and an increase in Factor V from 9% ± 4% to 69% ± 18% and Factor VII from 11% ± 5% to 71% ± 20%. Five responders with NANB hepatitis relapsed upon discontinuation of therapy, with recurrence of HE and increases in AST and PT, and improvement was observed upon retreatment. After 4 wk of intravenous therapy oral PGE2 was substituted. Two patients with NANB hepatitis recovered completely and remained in remission 6 mos and 12 mos after cessation of therapy. Two additional patients maintained in remission after 2mos and 6mos of PGE2. No relapses were seen in the patients with hepatitis A virus and hepatitis B virus infection. Liver biopsies in all 12 surviving patients restored to normal. In the five no n-responders an improvement in hepatic function was indicated by a fall in AST (3767U/L ± 2611U/L to 2142U/L ± 2040U/L), PT (52s ± 25s to 33s ± 18s), and PTT (103s ± 29s to 77s ± 44s), but all deteriorated and died of cerebral edema (*n* = 3) or liver transplantation (*n* = 2). These results suggest that PGE has beneficial effect on FHF.

According to the severity, hepatic failure was divided into early stage, typical symptom stage and late stage. A treatment group of 55 cases received PGE1 therapy and a control group received basic support therapy only. T he results showed that difference of the total effective rate was not significan t between these two groups, but in the early stage of hepatic failure, the effec tive rate in the treatment group was markedly higher than that in the control group. In addition, incidence of hepato-renal syndrome was lower in the treatment group[2]. This study indicates that division of severe viral hepatitis into three stages for evaluation of therapeutic effect is rational and useful and early use of PGE1 may certainly show some efficacy.

While orthotopic liver transplantation (OLT) has become the treatment of choice for most irreversible end-stage liver diseases, its role in patients with hepat itis B (HBV) infection is controversial. A high risk of reinfection of the trans planted graft, associated with significant morbidity and mortality, has been rep orted. Although passive and active immunization can delay the reappearance of virus in the allograft, there is not yet an effective therapy for recurrent HBV infection in liver transplant recipients. Twenty-eight OLT in 25 patients with acute and chronic HBV infections were performed[5]. Twelve of the patie nts were HBV DNA-negative, six were HBV DNA-positive, and seven were not teste d prior to transplantation. Only 19 patients surviving more than 100 days after transplantation were considered to have sufficient duration of follow-up (mean 734 days) to include in the analysis of recurrence. Five (26%) were fr ee of recurrent disease at the time of last follow-up (mean 1031 days). Rec urrent HBV in the allograft, as defined by positive immunoperoxidase stains of biopsy sections for viral antigens, was de tected in 74% at a mean of 134 d posttransplantation. Histological chang es of viral hepatitis were evident in 13 of 14 with positive immunostaining. Twelve o f the 14 patients were treated, on an open trial basis, with intravenous and ora l prostaglandin E (PGE) because of deteriorating clinical condition. Eleven of t he twelve responded to PGE with an initial drop in serum transaminases, improvem ent in coagulopathy and resolution of encephalopathy. One patient failed to resp ond and died of myocardial infarction within 9 d of institution of thera py. Three of the eleven patients with an initial response relapsed and died of liver failure as a direct result of recurrent HBV after 13 d, 16 d and 37 d of treat ment in association with generalized sepsis. Eight of the 12 patients (67%) had a sustained favorable response to PGE therapy (mean follow-up 737 days). All patients with a sustained response had accompanying improvement in histology and reduction in viral antigen staining in hepatocytes. Treatment with PGE appeared to be of benefit in recurrent HBV infection of the transplanted liver with an initial response rate of 92% and a sustained response rate of 67%.

The efficacy of PGE1 was demonstrated in the treatment of another 4 patients with subfulminant hepatitis of viral hepatitis B[6]. Three patients suff ered from hepatic enchepalopathy of the first degree, and the remaining one of t he second degree. In three patients the clinical and biochemical improvement cam e relatively quickly, followed by recovery. In one patient, due to drug intolera nce, the treatment was discontinued on the third day. The recurrence of illness was noted with the moderate increase of serum aminotransferase activities witho ut clinical deterioration, necessitating no further use of prostaglandin E1.

Bojic suggested that prostaglandin E1, applied in the treatment of patients with su bfulminant form of hepatitis, has favorable effect on the course of illness.

In a rare case of severe acute hepatitis A complicated by pure red cell aplasia (PRCA), plasma exchange transfusion and glucagon-insulin (GI) therapy improved the consciousness, but bilirubin, transaminase levels, and IgM anti-HAV titer remained high. Intravenous administration of lipophilized PGE1 (lipo-PGE1) was added to the GI therapy. Bilirubin and transaminase levels were n ormalized in the wk 8 after the initiation of this combination therapy (17 wk after admission). The combined use of lipo-PGE1 with plasma exchang e and GI therapy appeared to be useful for the severe hepatitis in this patient [7].

Two patients with HIV infection developed acute hepatitis B with liver insufficiency and hepatic encephalopathy. After alprostadil infusion was begun, they improved quickly and got a full recovery[8].

MECHANISMS OF HEPATIC CYTOPOTECTION OF PGE1

Indocyanine green disappearance enhanced by PGE1

Indocyanine green (ICG) is a reliable indicator reflecting hepatocyte function a nd hepatic blood flow. PGE1 has been indicated to increase hepatic blood flow and protect the hepatocyte. Tsukada[9] found that PGE1 administration increased ICG-K in the liver cirrhosis (LC) and chronic hepatitis (CH) groups with normal liver function, and the ICG-K response was dose depen dent when the dosage of PGE1 ranged from 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Inhibitory effects of PGE1 on T-cell mediated cytotoxicity

The effects of PG E1 on cell-mediated cytotoxicity against hepatocytes were investigated using *in vitro* cytotoxic assay system by Ogawa[10] . Isolated liver cells from normal C57BL/6 mice were used as the target ce lls, and effector cells were obtained from spleens of C57BL/6 mice in whic h experimental hepatitis had been induced by immunization with syngeneic liver a ntigens. In this assay system, spleen T cells adhering to nylon wool demonstrate d a high cytotoxic activity against target liver cells. The cytotoxicity was mar kedly reduced by PGE1 at concentrations greater than 10^{-7}mol/L. Maximum suppressive activity was obtained when PGE1 was continuously present during the assay period. By contrast, indomethacin, a specific inhibitor of prostaglandin synthes is, enhanced the cytotoxic activity of effector cells. These data seem to indica te that exogenously added PGE1 has an inhibitory effect on cell-medi ated cytotoxicity of effector spleen cells against target hepatocytes.

PGE1 enhance DNA synthesis of injured liver after partial hepatectomy by stimulating cyclic AMP production and increasing ATP level in hepatic tissue

D-galactosamine (D-gal) damaged rats were infused with PGE1 through peripheral vein for 40 min. before and after partial hepatectomy. DNA s ynthesis following 68% partial hepatectomy was severely inhibited by the pretrea tment of D-galactosamine. PGE1 infusion (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) enhanced the DNA synthesis inhibited by D-gal 600 mg/kg significantly (P <0.01). After 20 min of PGE1 infusion cyclic AMP levels of liver tissue was incre ased as compared with saline infusion in D-gal (600 mg/kg) damaged rat (P <0.05). Twenty min and 3 h after partial hepatectomy, ATP levels of liver tissue was enhanced in PGE1 treated group (P<0.05). These results suggest that PGE1 enhances DNA synthesis of injured liver after partial hepatectomy by the mechanism of stimulating cyclic AMP production and increasing ATP level in hepatic tissue[11].

PGE1 could accelerate the recovery of mitochondrial respiratory functio n after reperfusion, stabilization of membrane microviscosity

PGE1 has been indicated to increase hepatic blood flow and protect the hepatocyte. Kurokawa *et al*[12] found that PGE1 could accelerate the recovery of mitochondrial respiratory function after reperfusion. When PGE1 was continuously administered to rats from 24 h before giving a do se of carbon tetrachloride, deranged serum glutamic pyruvic transaminase levels and prothrombin time were significantly reduced 12 h after intoxication compared with controls. A similar effect of PGE1 was seen at 24 h in D-galactosamine-intoxicated rats. Liver histology showed a compara ble attenuation of injury in these rats. These results were consistent with repo rted effects of PGE2, suggesting that both prostaglandins may share a common pat hway in protection against liver injury. When PGE1 or 16,16'-dimethyl PGE2 was added to the medium of primary cultured rat hepatocytes, lipid peroxidation- dependent killing of the cells by tert-butyl hydroperoxide was significantly at tenuated without affecting the extent of malondialdehyde accumulation compared w ith controls. Both prostaglandins significantly reduced the extent of increased plasma membrane microviscosity of these cells. Masaki *et al*[13] con cluded that PGE1 and PGE2 may possess cytoprotective effects on liver parenchymal cells through stabilization of membrane microviscosity, which may contribute to protection against liver injury.

While the mechanisms of prostaglandin on protecting liver injury are not well understood, it has been demonstrated that dimethyl PGE2

abrogates the induction of tumour necrosis factor, leukotriene B4 (LTB4) and procoagulant activity by ma crophages as well as attenuating the expression of major histocompatibility clas s antigens on the surface of hepatocytes, and may inhibit viral replication. Fro m the present research, we came to a conclusion that increasing hepatic blood flow, accelerating the recovery of mitochondrial respiratory function after reperfusion, stabilizing the membrane microviscosity, decreasing the cell-medi ated cytotoxicity against hepatocytes, enhancing DNA synthesis by stimulating cyclic AMP production and increasing ATP level in hepatic tissue made PGE1 as a hepatic cytoprotective agent.

TOXIC EFFECTS OF INTRAVENOUS AND ORAL PGE THERAPY ON PATIENTS WITH LIVER DISEASE

Prostaglandins are cytoprotective agents that have been shown to benefit patients with a variety of acute and chronic liver diseases. Few data exist on the freq uency of adverse effects of prostaglandins in these patients. Cattral *et al*[14] retrospectively studied 105 patients with liver disease who were treated with either i.v. or oral PGE. Forty-four patients with primary nonfun ction after liver transplantation and 36 patients with fulminant hepatic failure received i.v. PGE1 for 4.5 d ±2.6 d and 12.6 d ±10.9 d, respectively. Twenty-five patients with recurrent hepatitis B viral infection after liver transplantation received oral PGE1 for 105 d ± 94 d or PGE2 for 464 d ± 399 d. Twenty-six of 80 patients (33%) receiving i.v. PGE1 developed gastrointest inal and/or cardiovascular side effects and 8% developed arthritis. Twenty-thre e (92%) of 25 patients who received high-dose oral PGE1 or PGE2 incurred arthritis and/or gastrointestinal adverse effects. Twenty-five patients receive d prolonged PGE therapy (oral >60d; i.v. >28d). Of this group , 23 (92%) developed clubbing and cortical hyperostosis resembling hypertrophic osteoarthropathy. All adverse effects were dose related and resolved with reduction or cessation of therapy. PGE therapy resulted in a wide spectrum of multisys tem adverse effects which were reversible with reduction or cessation of therapy . Although the administration of PGE was safe and generally well tolerated, clos e medical supervision is necessary to avoid serious side effects.

RECENT ADVANCES IN LIPID MICROSPHERE TECHNOLOGY FOR TARGETING PROSTAGLANDIN DELIVERY

Although PGE1 exhibits pharmacological activities in free for m, it has been hypothesized and experimentally verified that carrier can targe t them more effectively at lower doses, thus causing fewer side effects. Lipid microspheres (LM) with a diameter of 0.2 μm are drug carriers prepared from soybean oil and lecithin, and the drug is incorp orated within the LM. Lipo-PGE1 is LM preparations of PGE1 that are designed to accumulate at the vascular lesions. The newly developed lipo-PGE1 (lipo-AS013) could overcome the disadvantages of the preparation currently available[15]. Lipo-AS013, a precursor of PGE1, is considered superior to free PGE1 in terms of its chemical stability and the retention ratio in LM in the body.

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