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Leukotriene D4 mediates galactosamine/endotoxin-induced hepatitis in mice

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Introduction

Leukotrienes are potent mediators in the inflammatory response (reviewed in ref.1). It was also shown that the liver is able to produce peptidoleukotrienes following an endotoxin stimulus and to secrete them into the bile (2). We recently showed in a galactosamine/endotoxin (GalN/E) intoxication model in the mouse that different pharmacological interventions on the leukotriene synthesis pathway prevented GalN/E-induced hepatitis whereas prostanoid synthesis inhibitors had no effect (3). In addition, we observed that chemical depletion of hepatic glutathione by pretreatment of the animals with phorone completely protected against GalN/E-induced hepatitis. Therefore we concluded that a glutathione-derived leukotriene species might be the ultimate pathogenic metabolite in GalN/E hepatitis. The aim of this study was to support direct experimental proof for this view.

Effect of intravenously injected leukotrienes on the development of hepatitis in mice sensitized by galactosamine

Treatment	S G P T
Untreated control	70 ± 30
GalN/E	6120 ± 4820*
GalN	80 ± 20
Endotoxin	70 ± 30
GalN/LTD_4	6190 ± 4290*
LTD_4	60 ± 10
GalN/LTE_4	150 ± 85
LTE_4	140 ± 20

*p 0.001 compared to untreated control
n = 6-9
Doses: 700 mg/kg galactosamine;
33 μg/kg endotoxin (E);
50 μg/kg leukotrienes 1 hour after GalN.
SGPT: serum alanine aminotransferase activity in U/liter.

Results and Discussion

When male NMRI mice received 700 mg/kg galactosamine (Serva, Heidelberg) and one hour later 33 μg/kg Salmonella abortus equi endotoxin (Sigma Chemicals), they developed a fulminant hepatitis within nine hours as assessed by serum transaminase activities. If the order of the intraperitoneal injections was reversed, essentially no liver injury was detectable (n=8). Likewise, inhibition of the catabolism of LTC_4 by intravenous pretreatment of the animals with 50 mg/kg of the glutamyltranspeptidase inhibitor AT 125 (Upjohn) 90 min. prior to GalN/E completely prevented hepatitis. These observations prompted us to inject intravenously different leukotrienes (ICN Biochemicals) to mice which had been sensitized by i.p. GalN injections one hour before. The results in the table demonstrate that it is specifically the combination of GalN and LTD_4 which led to the development of a severe liver injury comparable to the one produced by GalN/E. In contrast, neither the two leukotrienes studied had any significant hepatotoxic effect, nor GalN or endotoxin when given alone.

Our results offer a new perspective for the understanding of the pathophysiology of the liver. Moreover, these observations provide a means for the in vivo screening of leukotriene synthesis inhibitors in the GalN/E model and the identification of leukotriene antagonists in the GalN/LTD_4 model.

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