Comparative Hepatology

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Proceedings

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The regulatory role of prostaglandin E_2 in liver (patho) physiology is controlled at its site of synthesis and its action on the receptors

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from 11th International Symposium on the Cells of the Hepatic Sinusoid and their Relation to Other Cells
Tucson, Arizona, USA, 25–29 August, 2002

Published: 14 January 2004

Comparative Hepatology 2004, **3**(Suppl 1):S35

This article is available from: http://www.comparative-hepatology.com/content/3/S1/S35

Introduction

Among the hormone class of the eicosanoids, PGE_2 plays a predominant role in liver (patho) physiology. Liver-specific responses, like regulation of blood glucose homeostasis, sinusoidal blood flow within the liver, properties of the transendothelial barrier within the liver, synthesis and release of important other mediators like cytokines, growth factors or nitric oxide, and liver fibrogenesis have been shown to be mediated or regulated by PGE_2 [1]. Within the liver, the main producers of PGE_2 are the Kupffer cells. The synthesis of PGE_2 in Kupffer cells is controlled at multiple levels. The action of PGE_2 on its target cells is mediated by 4 classes of PGE_2 receptors (EP1, EP2, EP3, EP4). Each of these receptors converts the information of PGE_2 by different intracellular signal pathways to a specific cellular response [2].

Methods

Liver nonparenchymal cells (endothelial cells, Kupffer cells, stellate cells) are isolated from male rat livers by a pronase/collagenase perfusion. Experiments are performed with cells kept in primary cultures [1].

Results and Discussion

Isolated liver nonparenchymal cells (endothelial cells, Kupffer cells, stellate cells) are characterized by different markers (Table 1).

Table 1: Characterization of endothelial cells (EC), Kupffer cells (KC) and stellate cells (SC) by different markers.

Marker	ED-1	Latex Beads	Ac-LDL	vWF	Reca -1	CD 31	SMA	Desmin
EC	neg	neg + pos	neg + pos	pos	pos	pos	neg	neg
KC	pos	pos	pos	neg	neg	neg	neg	neg
SC	neg	neg	neg	neg	neg	neg	pos	pos

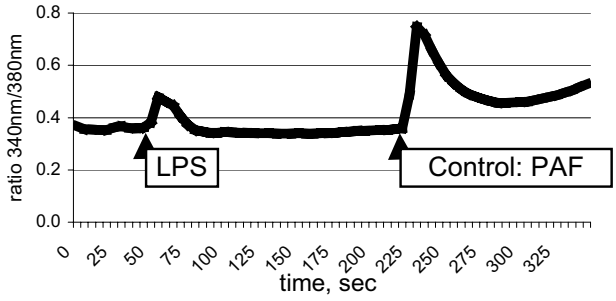

Figure 1
Intracellular free calcium after LPS and platelet activating factor (PAF).

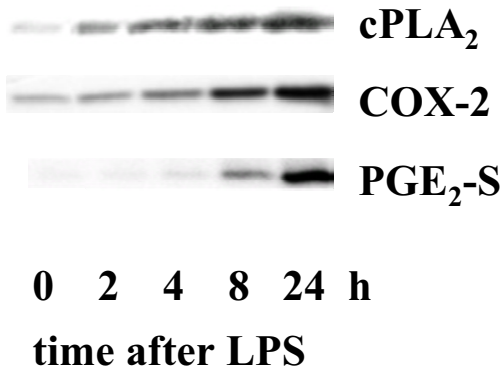

Figure 2
LPS-induced expression of $cPLA_2$, COX-2 and PGE_2-synthase (S).

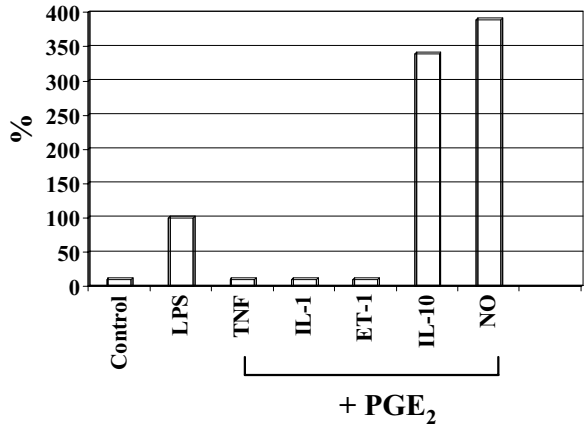

Figure 3
Effect of PGE_2 on LPS-induced formation of TNF-alpha, IL-1, ET-1, IL-10 and NO.

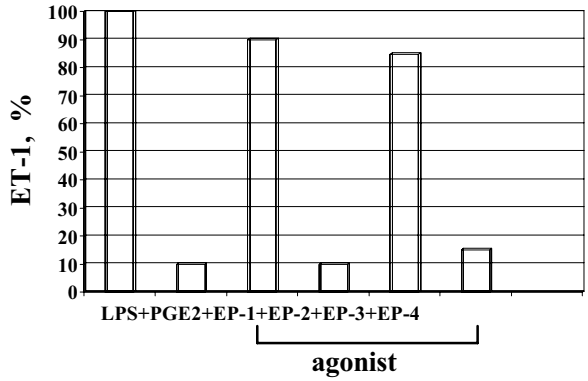

Figure 4
Effect of PGE_2-receptor agonists (EP -1/-2/-3/-4) on LPS-induced release of ET-1.

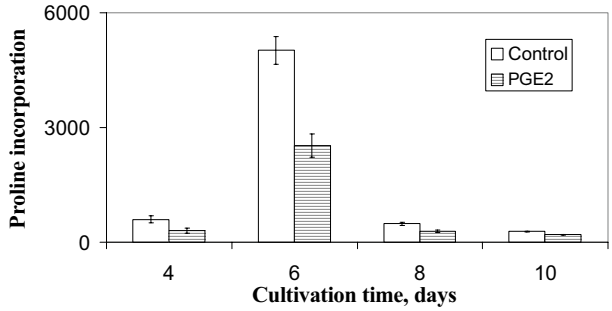

Figure 5
Effect of PGE_2 on collagen synthesis (proline incorporation) in stellate cells.

The fast synthesis of PGE_2 in Kupffer cells (induced by, e.g., platelet activating factor, zymosan, calcium ionophore) requires a sustained increase of cellular calcium (Fig. 1). The delayed synthesis of PGE_2 in Kupffer cells (induced by, e.g., LPS) is paralleled by a transient increase of cellular calcium (Fig. 1), and requires a *de novo* / enhanced expression of cytosolic phospholipase A_2 ($cPLA_2$), cyclooxygenase (COX)- 2 and PGE_2 synthase (Fig. 2).

Besides eicosanoids, LPS induces in Kupffer cells the release of other mediators, including IL-1, IL-10, TNF-alpha, ET-1, and NO (1). The release of IL-1, TNF-alpha and ET-1 is totally suppressed by PGE_2, the release of IL-10 and NO (1) is enhanced by PGE_2 (Fig. 3). The regulation of the synthesis of IL-1, IL-10, TNF-alpha (Fig. 4) and ET-1 in Kupffer cells by PGE_2 is mediated by EP-2 and EP-4, as demonstrated by the use of PGE_2-receptor-specific agonists (EP-1/-2/-3/-4:ONO-DI-004/-AE1-259/-AE-248/-AE1-329).

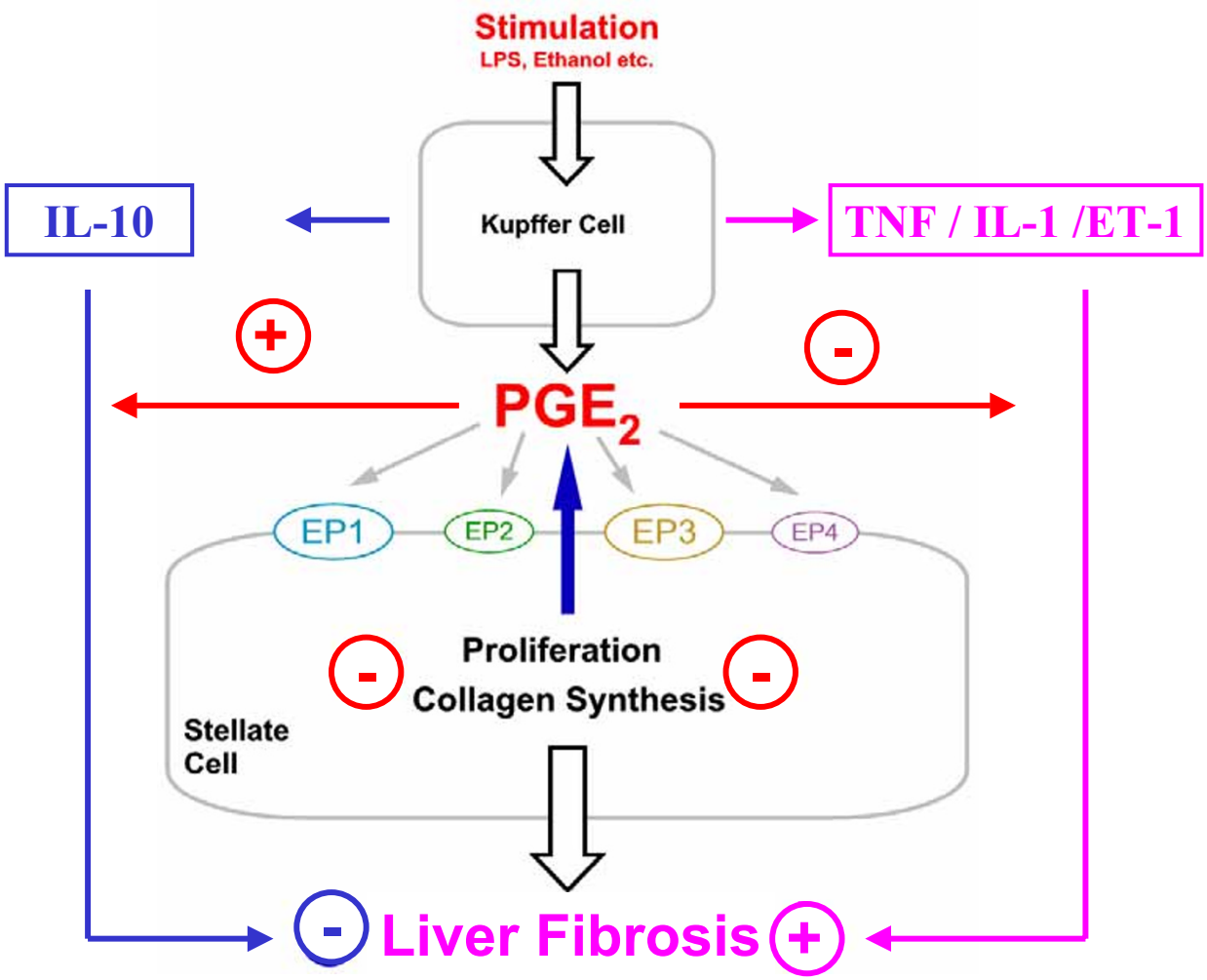

Figure 6
PGE_2: A potent physiological suppressor of liver fibrosis.

PGE_2 inhibits proliferation, transdifferentiation and collagen synthesis (Fig. 5) of Stellate cells.

Conclusions

PGE_2, produced by Kupffer cells, is a potent physiological suppressor of liver fibrosis (Fig. 6).

References

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2. Fennekohl A, Segi E, Sugimoto Y, Ichikawa A, Püschel GP: **Parallel action of EP2 and EP4 receptor for the prostaglandin E_2-mediated feedback inhibition of the LPS-induced TNF-alpha formation in mouse Kupffer cells.** In: *Cells of the Hepatic Sinusoid Volume 8*. Edited by: *Wisse E, Knook DL, de Zanger R, Arthur MJP. Leiden, Kupffer Cell Foundation*; 2001:11-14.