

The regulatory role of prostaglandin E₂ in liver (patho) physiology is controlled at its site of synthesis and its action on the receptors

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Introduction

Among the hormone class of the eicosanoids, PGE₂ 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 PGE₂ [1]. Within the liver, the main producers of PGE₂ are the Kupffer cells. The synthesis of PGE₂ in Kupffer cells is controlled at multiple levels. The action of PGE₂ on its target cells is mediated by 4 classes of PGE₂ receptors (EP1, EP2, EP3, EP4). Each of these receptors converts the informa-

tion of PGE₂ 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

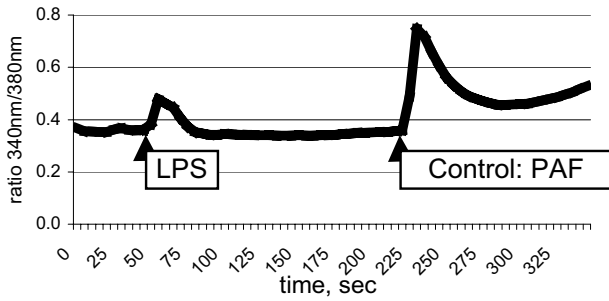


Figure 1
Intracellular free calcium after LPS and platelet activating factor (PAF).

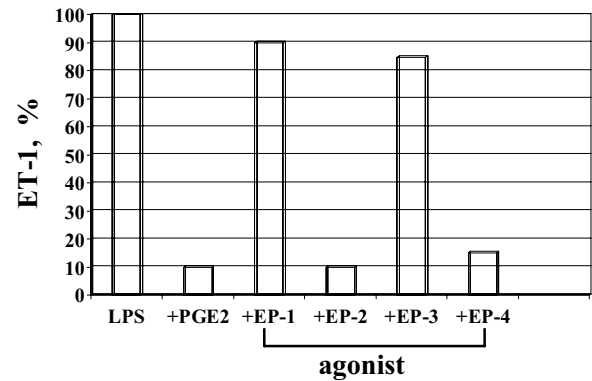


Figure 4
Effect of PGE₂-receptor agonists (EP -1/-2/-3/-4) on LPS-induced release of ET-1.

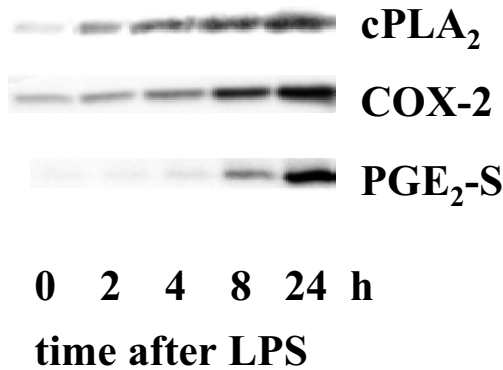


Figure 2
LPS-induced expression of cPLA₂, COX-2 and PGE₂-synthase (S).

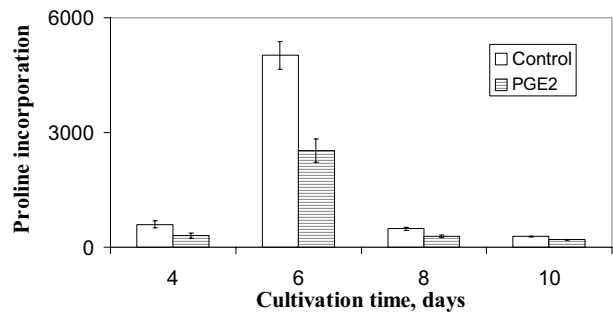


Figure 5
Effect of PGE₂ on collagen synthesis (proline incorporation) in stellate cells.

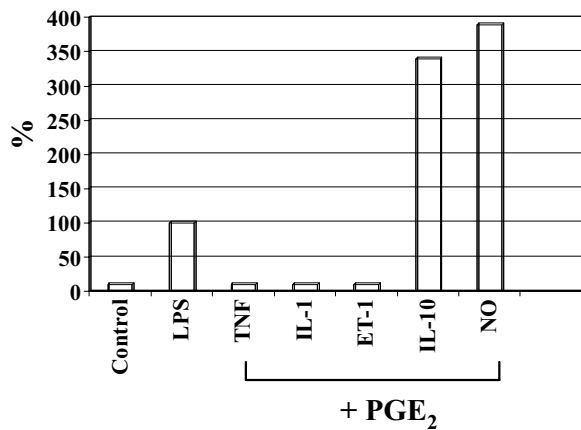


Figure 3
Effect of PGE₂ on LPS-induced formation of TNF-alpha, IL-1, ET-1, IL-10 and NO.

The fast synthesis of PGE₂ 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 PGE₂ 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 A₂ (cPLA₂), cyclooxygenase (COX)- 2 and PGE₂ 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 PGE₂, the release of IL-10 and NO (1) is enhanced by PGE₂ (Fig. 3). The regulation of the synthesis of IL-1, IL-10, TNF-alpha (Fig. 4) and ET-1 in Kupffer cells by PGE₂ is mediated by EP-2 and EP-4, as demonstrated by the use of PGE₂-receptor-specific agonists (EP-1/-2/-3/-4:ONO-DI-004/-AE1-259/-AE-248/-AE1-329).

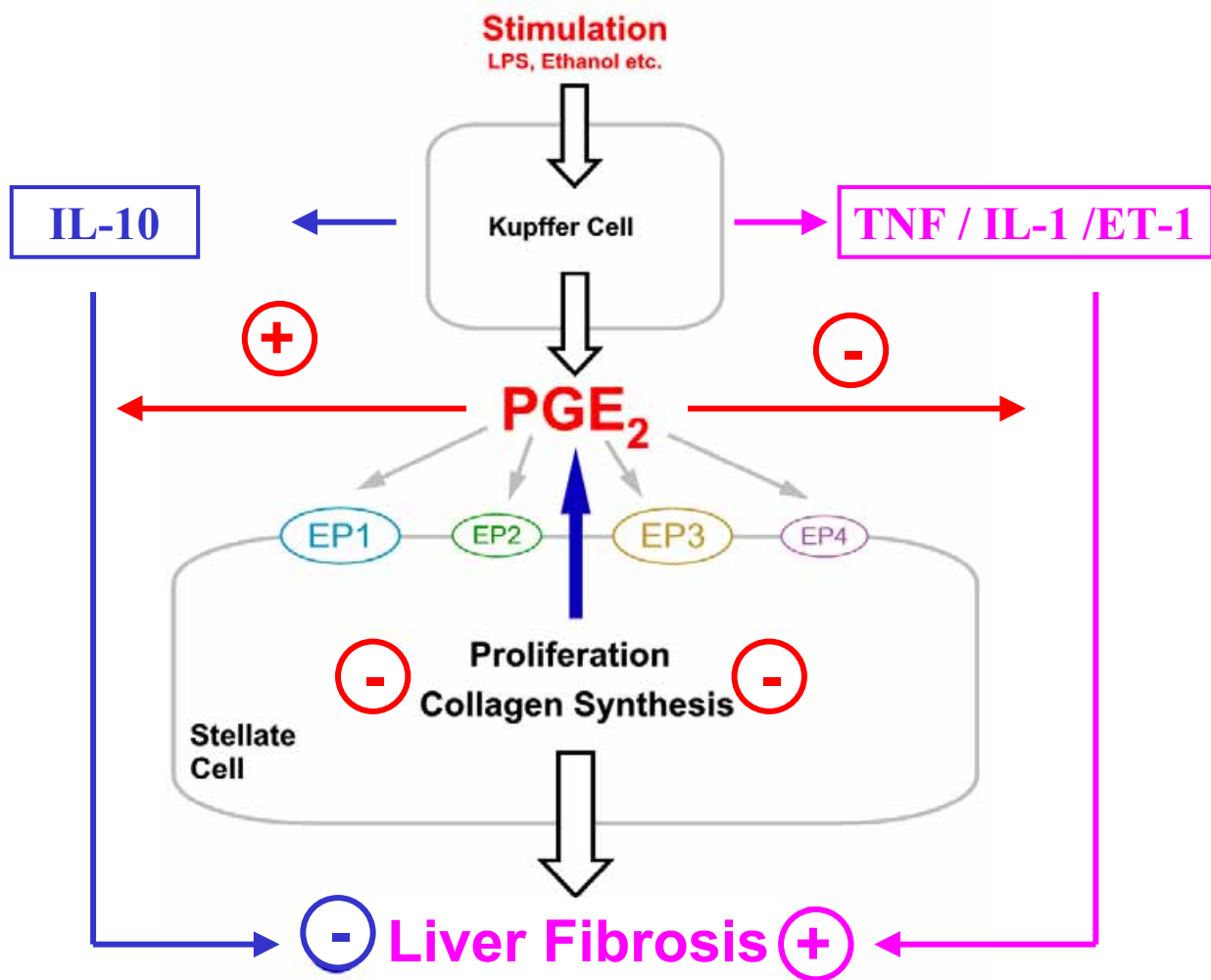


Figure 6
 PGE₂: A potent physiological suppressor of liver fibrosis.

PGE₂ inhibits proliferation, transdifferentiation and collagen synthesis (Fig. 5) of Stellate cells.

Conclusions

PGE₂, produced by Kupffer cells, is a potent physiological suppressor of liver fibrosis (Fig. 6).

References

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