EFECTES DELS INHIBIDORS DE LA CICLOOXIGENASA EN CÈL·LULES HEPÀTIQUES I EL SEU PAPER EN LA INFLAMACIÓ I FIBROSI HEPÀTICA EXPERIMENTAL

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Annex

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Liver: The formation and actions of aspirin-triggered lipoxins ☆

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Abstract

Eicosanoids play a key role in the initiation, progression and resolution of the inflammatory response. Although most current anti-inflammatory strategies are focused on the pharmacological inhibition of pro-inflammatory eicosanoids, such as prostaglandins and leukotrienes, mounting evidence indicates the existence of potent endogenous eicosanoids able to control inflammation and orchestrate its resolution. The first eicosanoids recognized as anti-inflammatory compounds generated by our own organism were the lipoxins (LXs). More recently, a new series of carbon-15 epimers of LXs, with anti-inflammatory properties similar to those of native LXs, was identified during aspirin treatment. Since their formation is specific to this venerable non-steroidal anti-inflammatory drug, the term aspirin-triggered LXs (ATLs) was coined for these compounds. This chapter deals with the biosynthesis of LXs and ATLs in the liver, the largest solid organ/gland in the body, and discusses the most relevant actions of these lipid mediators in the context of liver inflammation and injury.

1. The hepatic sinusoid

The liver contains a complex architecture composed of several cell types. To ensure full hepatic functionality, hepatocytes, which represent about 70% of liver cell population, are arranged within the hepatic lobule in a peculiar fenestrated capillary network known as the hepatic sinusoid [1]. The morphological features of the hepatic sinusoid provide a unique environment where each single hepatocyte is in close contact with other hepatocytes as well as with sinusoidal cells. Liver sinusoidal cells, also known as non-parenchymal liver cells, consist of three different cell types: endothelial cells, Kupffer cells and hepatic stellate cells [1]. In the sinusoid, endothelial cells make up the sinusoidal lining as a selective physical barrier between the blood and the space of Disse, which works as a continuous basement membrane of the endothelium [2]. The main characteristic of the sinusoidal endothelium is that it is provided with numerous fenestrae that allow direct communication between the sinusoidal lumen and the space of Disse [2]. On the other hand, Kupffer cells, the liver macrophages, lie in the sinusoidal lining in direct contact with the blood and represent the most important population of resident macrophages in the body. Because of their macrophage lineage, Kupffer cells have been classically considered the major sinusoidal cell type involved in eicosanoid formation in the liver [3]. In fact, Kupffer cells express key eicosanoid-generating enzymes, including cyclooxygenase (COX)-1, COX-2 and 5-lipoxygenase (5-LO), and generate relevant amounts of prostanoids (prostaglandin (PG) E_2, PGI_2, $PGF_{2\alpha}$, thromboxane (TX) B_2 and PGD_2, the latter being the major COX-derived product) and leukotrienes (LTB_4 and $LTC_4/LTD_4/LTE_4$) [3–5]. Finally, hepatic stellate cells, which have characteristics of both fibroblasts and myofibroblasts, are located in the space of Disse between hepatocytes and endothelial cells [1,2].

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2. Biosynthesis of lipoxins and aspirin-triggered lipoxins in the hepatic sinusoid

Lipoxins (LXs) are conjugated trihydroxytetraene-containing eicosanoids generated through cell–cell interactions by a process known as *transcellular biosynthesis* [6]. *Transcellular metabolism* is a common finding in eicosanoid formation and involves the processing of a metabolic intermediate generated by one cell (donor cell) by a vicinal cell (acceptor cell) for the production of an active eicosanoid which neither cell can generate alone [7,8]. In mammals, a major route of transcellular LX biosynthesis involves the sequential interaction of a 15-lipoxygenase (LO) and a 5-LO. 15-LO-initiated LX production is clearly demonstrated in airway epithelial cells, monocytes and eosinophils, in which 15-LO is up-regulated by anti-inflammatory cytokines such as interleukin (IL)-4 and IL-13 [6]. Once activated, these cells generate and release 15*S*-hydroxyeicosatetraenoic acid (15*S*-HETE), which is rapidly taken up and converted to LXs by 5-LO [9]. A similar transcellular route of LX biosynthesis has been recognized in the liver. In the hepatic sinusoid, 15*S*-HETE released by nearby 15-LO-containing hepatocytes is converted to LXs by Kupffer cells, which are the only sinusoidal cell type endowed with 5-LO activity (Fig. 1) [10]. In fact, HPLC analysis of materials obtained from coincubations of hepatocytes and liver sinusoidal cells reveals the presence of a strong UV absorbance at 300 nm within the LX region, the elution profile of which is consistent with that of synthetic LXA_4 [10].

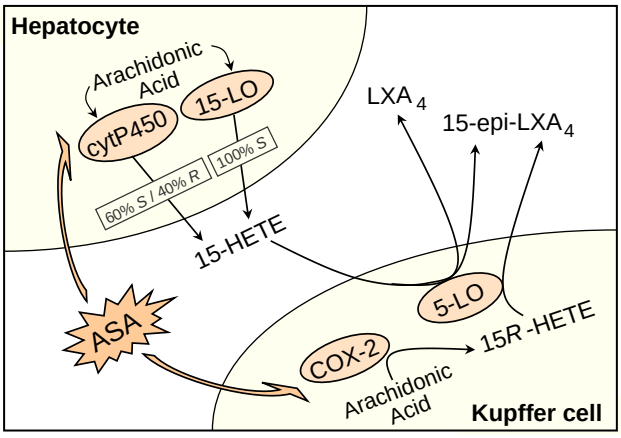

Fig. 1. Biosynthetic pathways of lipoxin (LX) and 15-epi-LX formation in liver cells. A first circuit of transcellular LXA_4 and 15-epi-LXA_4 biosynthesis involves the conversion of hepatocyte-derived 15-hydroxyeicosatetraenoic acid (15-HETE) by 5-lipoxygenase (5-LO) in Kupffer cells. In the hepatocyte, the formation of 15-HETE is stereoselective (60% S and 40% *R*) and appears to be the result of the oxygenation of arachidonic acid by the cytochrome P450 system. Indeed, the cytochrome P450 is the most significant pathway of arachidonic acid metabolism in hepatocytes and its activity can be up-regulated by aspirin (ASA). Hepatocyte 15*S*-HETE may also originate from 15-LO, since this enzyme has been localized by immunocytochemistry in parenchymal liver cells. On the other hand, generation of 15-epi-LXA_4 from endogenous sources of arachidonic acid can also occur in the hepatic sinusoid through the sequential actions of ASA-acetylated COX-2 and 5-LO in a single cell type (i.e. Kupffer cells).

Another major route of transcellular LX biosynthesis is the generation of 15-epi-LXs through a circuit initiated by acetylation of COX-2 by aspirin (ASA) [11]. In this route, when ASA inhibits PG formation in cells bearing a cytokine-induced COX-2, the resulting ASA-acetylated COX-2 converts arachidonic acid into 15*R*-HETE. In an inflammatory scenario and during the interaction of vascular endothelial or epithelial cells with neutrophils, 15*R*-HETE is subsequently transformed by 5-LO of activated neutrophils to a new class of 15-epi-LXs that carry the carbon-15 alcohol in the *R* configuration, instead of the *S* as in the native LXs [6,11,12]. These 15-epi-LXs, also termed aspirin-triggered LXs (ATL), are specifically generated during ASA treatment, and are considered to mediate, at least in part, some of the beneficial actions of this non-steroidal anti-inflammatory drug (NSAID). ASA is the leading NSAID and is widely used for relieving inflammation and mild to moderate pain and fever. Low-dose ASA is also used as an anti-thrombogenic agent for prevention of myocardial infarction and exerts significant protection from sporadic colon cancer [13,14]. During ASA intake, the active compound, acetylsalicylic acid, is absorbed from the upper small intestine and rapidly pre-systemically metabolized by enzymatic hydrolysis on its first pass through the portal circulation [15]. Within the liver, ASA is hydrolyzed by esterases abundant in parenchymal liver cells and specifically in hepatocyte mitochondria and endoplasmatic reticulum [16,17]. Liver cells also convert most of the salicylate to water-soluble conjugates (i.e. ester and ether glucuronides, salicyluric acid and gentisic acid), which are rapidly cleared by the kidneys [16,17]. Because all blood draining the gastrointestinal tract enters the liver via the portal vein and about 73% of ASA is converted to salicylate within 30 min of its ingestion [18], the concentration of acetylsalicylic acid in the liver probably exceeds that in serum and other tissues. Therefore, it seems reasonable to conceive that the impact of this acetylating NSAID on the formation of ATL is higher in hepatic cells than in any other cell type. Indeed, in our laboratory we have demonstrated that liver tissue from animals receiving ASA is a rich source of 15-epi-LXA_4 [10].

The exact sequence of events leading to ATL biosynthesis in the liver is, at present, not completely understood. In the hepatic sinusoid, formation of ATL from endogenous sources of arachidonic acid appears to occur in a single cell type [5]. Indeed, relevant amounts of ATL have been detected during the incubation of Kupffer cells with ASA [5]. These liver macrophages have both COX-2 and 5-LO in place, and generate

15-epi-LXA_4 through the sequential actions of ASA-acetylated COX-2 and 5-LO (Fig. 1). Interestingly, an inverse relationship has been observed between PGE_2 and 15-epi-LXA_4 levels in Kupffer cells exposed to ASA (Fig. 2a) [5]. This effect is specific to ASA and was not observed, for example, with the selective COX-2 inhibitor celecoxib. Formation of LXs from endogenous arachidonic acid in a single cell type is a common event in granulocytes and macrophages isolated from asthmatic patients [19] as well as in neutrophils from patients with liver cirrhosis [20].

Formation of ATL in the liver may also arise from transcellular routes. In this regard, rat hepatocytes exposed to ASA switch eicosanoid class formation from the predominant COX-derived product TXB_2 to 15-HETE (Fig. 2b) [10]. Hepatocyte-derived 15-HETE, which carries a racemic carbon-15 position (i.e. a mixture of 15*S*- and 15*R*-HETE), is subsequently transformed by Kupffer cell 5-LO to both LXA_4 and 15-epi-LXA_4 (Fig. 1) [10]. This effect is specific for ASA, and it is not observed with other NSAIDs such as indomethacin, ibuprofen, valeryl salicylate or nimesulide. Since adult rat hepatocytes lack COX-2 expression [10], other sources of 15*R*-HETE different from ASA-acetylated COX-2 have been implicated. A role for the cytochrome P450 system has been proposed based on the following evidence: (i) the cytochrome P450 is the most significant pathway of arachidonic acid metabolism in hepatocytes [21], (ii) ASA is a well-known stimulus of cytochrome P450 activity in isolated rat hepatocytes [22,23], (iii) oxygenation of arachidonic acid by cytochrome P450 results in the stereoselective formation of 15-HETE (40% *R* and 60% *S*) (Fig. 1) [24], and (iv) adult human liver microsomes metabolize arachidonic acid by the cytochrome P450 system and form 15-HETE, predominantly on the *R* configuration [25]. Moreover, in hepatocytes, ASA-induced 15*R*/*S*-HETE formation is abrogated by proadifen (SKF 525A), a selective inhibitor of cytochrome P450-dependent arachidonate metabolism [26].

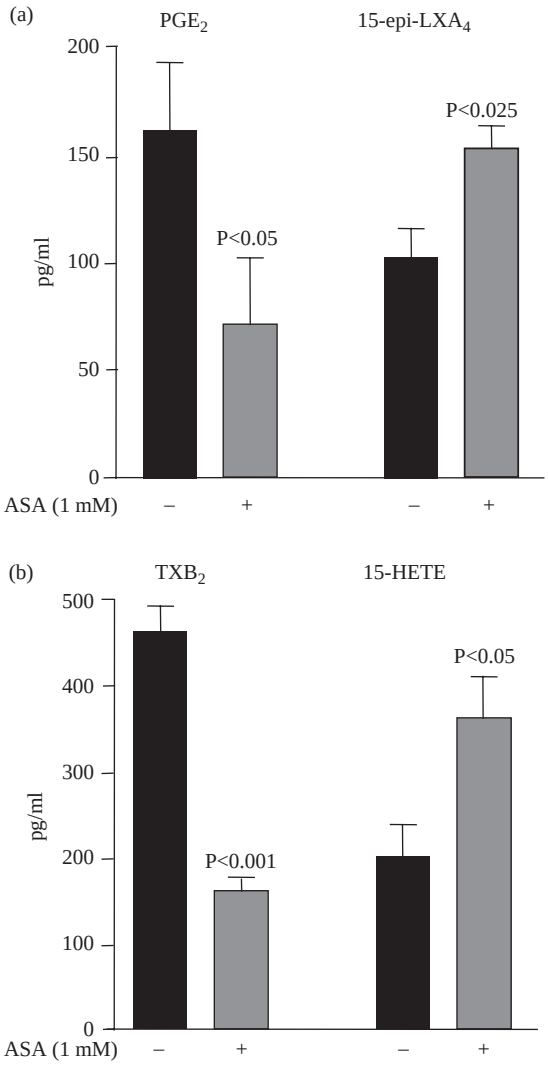

Fig. 2. Switching of eicosanoid class biosynthesis by aspirin (ASA) in liver cells. Isolated rat Kupffer cells (a) and hepatocytes (b) were exposed to ASA (1 mM) or vehicle for 40 min at 37 °C and prostaglandin (PG) E_2, 15-epi-lipoxin (LX) A_4, thromboxane (TX) B_2 and 15-hydroperoxyeicosatetraenoic acid (15-HETE) levels determined by enzymeimmunoassay.

3. Hepatic actions of LXs and ATL

Unlike other 5-LO products (i.e. LTs), which are pro-inflammatory and facilitate neutrophil adhesion to the vascular wall and recruitment at the site of inflammation and leukocyte respiratory burst and degranulation [27], LXs and ATL display inhibitory activities in leukocytes promoting resolution [6]. In human neutrophils, LXs and ATL and their stable analogs act as "stop-signals" for inflammation and inhibit chemotaxis, selectin- and integrin-mediated adhesion to and transmigration across endothelial monolayers in response to LTB_4 and formyl-methionyl-leucyl-phenylalanine [28,29]. Interestingly, LXs and ATL inhibit epithelial cell proliferation and angiogenesis [12,30]. In vivo, LX stable analogs inhibit LTB_4-induced leukocyte rolling and adherence and neutrophil margination and extravasation and when applied topically to mouse ears they dramatically inhibit leukocyte infiltration and vascular permeability [31,32]. ATL analogs protect mice from renal ischemia-reperfusion injury and glomerulonephritis [33]. In an animal model of periodontal disease, LX and ATL analogs attenuate gingivitis and leukocyte recruitment [34]. LX and ATL stable analogs attenuate airway hyperreactivity and accelerate resolution of pulmonary edema in a murine model of asthma [35] and suppress neutrophil inflammation and attenuate disease severity in a mouse model of chronic airway inflammation and infection associated with cystic

fibrosis [36]. Finally, ZK-192, a β-oxidation-resistant LXA4 analog with enhanced chemical stability and oral pharmacokinetics, potently attenuates hapten-induced colitis in rats [37]. Thus, with all these data in hand, it can be anticipated that the formation of LXs and ATL by liver cells may have significant physiological implications in this organ.

Like most eicosanoids, LXs and ATL are rapidly generated and metabolized in their local milieu. Therefore, once generated in the hepatic sinusoid, these anti-inflammatory compounds are expected to function as lipid autacoids exerting rapid and potent actions on nearby liver cells. Results from the authors' laboratory indicate that 5-LO activity in liver macrophages is inhibited by LXA_4 (Fig. 3) [5], an effect similar to that exerted by PGE_2 in human neutrophils [38]. These findings suggest that LXs also play an active role in the switching of eicosanoid classes, possibly during resolution of inflammation, and may have a major impact in dampening leukocyte-mediated inflammation in acute liver injury.

A role for ATL in modulating transcriptional factors implicated in the control of hepatic inflammation and injury has been established. One group of such transcriptional regulators is the peroxisome proliferator-activated receptor (PPAR) family. PPARs are ligand-activated transcription factors with a DNA binding domain that recognizes response elements in the promoter region of specific target genes linked to inflammation, cell proliferation, apoptosis and differentiation [39]. We have recently demonstrated that 15-epi-LXA_4 significantly inhibits PPARα protein expression in rat hepatocytes, an effect that is also observed when these parenchymal liver cells are exposed to ASA (Fig. 3) [5]. In contrast, hepatocyte PPARα levels are not modified by PGE_2 alone or in association with LTB_4 [5].

In addition to modulating the expression of key transcriptional factors, ATL also regulate the cytokine–-chemokine axes in hepatic cells. In our laboratory, we have found that unlike LTB_4 and PGE_2, 15-epi-LXA_4 significantly attenuates cytokine-induced neutrophil chemoattractant-1 (CINC-1) secretion by rat hepatocytes (Fig. 3) [5]. CINC-1, the rat counterpart of human IL-8, is an 8-kDa pro-inflammatory peptide and member of the C-X-C family of chemokines with potent chemotactic activity toward neutrophils [40]. These findings are consistent with previous investigations showing inhibition of IL-8 release in enterocytes, fibroblasts, human colon ex vivo and intestinal epithelia by LXA_4 and 15-epi-LXA_4 and their stable analogs [41–43].

4. Future directions

Considering the anti-inflammatory properties of LXs and ATL and the availability of potent and stable

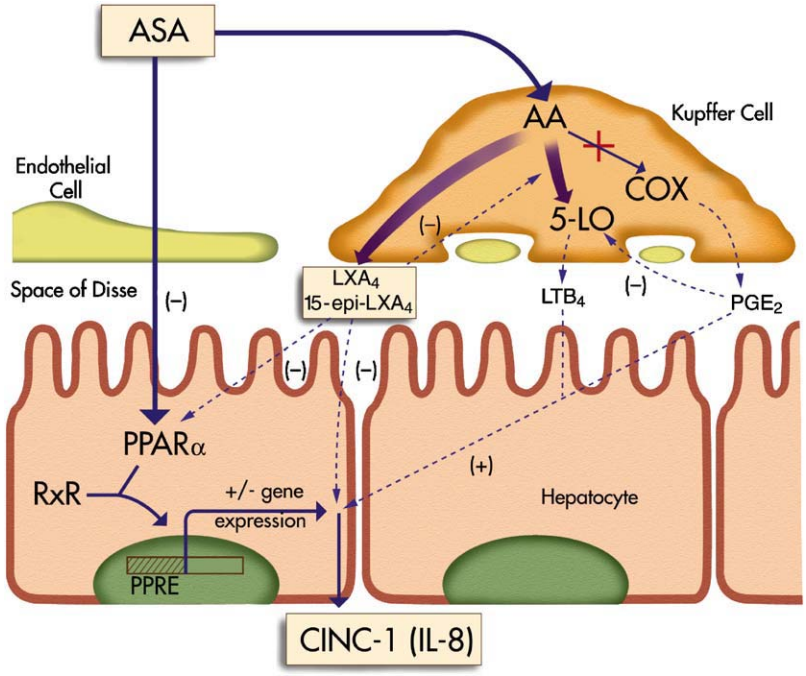

Fig. 3. Actions of lipoxin A_4 (LXA_4) and aspirin (ASA)-triggered 15-epi-LXA_4 in rat sinusoidal liver cells. LXA_4 and 15-epi-LXA_4 generated by Kupffer cells alone or in cooperation with nearby hepatocytes, display relevant activities in the hepatic sinusoid, including inhibition of cytokine-induced neutrophil chemoattractant-1 (CINC-1) secretion in hepatocytes, reduction of 5-lipoxygenase (5-LO) activity in liver resident macrophages and down-regulation of hepatocyte peroxisome proliferator-activated receptor (PPAR)α. This latter effect is also observed with ASA. In contrast, Kupffer cell-derived leukotriene (LT) B_4 and prostaglandin (PG) E_2 up-regulate CINC-1 production in adjacent hepatocytes. Reprinted with permission from Ref. [5].

analogs, further studies are warranted to test the therapeutic potential of these compounds in experimental models of liver disease. In addition, it is interesting to characterize the hepatic formation and actions of other recently identified endogenous anti-inflammatory systems, such as those originated from the ω-3 polyunsaturated fatty acids EPA and DHA, termed resolvins [44]. Since resolvins use a different substrate than LXs and ATL, the potential synergism between these two families of lipid mediators sharing function similarity remains to be determined.

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