Clinica Chimica Acta 413 (2012) 1817–1821

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Autotaxin in liver fibrosis

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ARTICLE INFO

Article history:
Received 4 June 2012
Received in revised form 3 July 2012
Accepted 6 July 2012
Available online 20 July 2012

Keywords:
Autotaxin
Lysophospholipase D
Liver fibrosis
Lysophosphatidic acid

ABSTRACT

Autotaxin (ATX) hydrolyzes lysophosphatidylcholine to produce lysophosphatidic acid (LPA), a multi-functional bioactive lipid mediator. ATX is a major determinant of LPA levels in the blood, and the pathophysiological functions of ATX are thought to be largely attributed to its ability to produce LPA. Liver fibrosis is one of the rare disorders exhibiting the increased ATX and LPA levels in the blood. This review summarizes the recent findings on the relation between ATX or LPA and liver fibrosis, the usefulness of serum ATX levels to predict the stages of liver fibrosis, and speculated roles of increased serum ATX and plasma LPA levels in liver fibrosis.

Contents

1. Autotaxin lysophospholipase D activity and lysophosphatidic acid production

Lysophosphatidic acid (1- or 2-acyl-lysophosphatidic acid; LPA) elicits a wide variety of biological responses including cell migration, neurogenesis, angiogenesis, smooth-muscle contraction, platelet aggregation, and wound healing [1,2]. Because it is present in blood at a concentration of ~0.1 μmol/L [3], ie, close to the concentration that exerts various effects on cells *in vitro* [1,2], LPA is regarded as a circulatory paracrine mediator. A major portion of LPA in blood is generated by lysophospholipase D (lysoPLD) from lysophospholipids, mainly lysophosphatidylcholine [4]. When cloned, lysoPLD was unexpectedly found to be identical to autotaxin (ATX).

ATX was originally discovered in conditioned medium from A2058 human melanoma cell cultures and was characterized as a stimulator of cell migration [5]. Since then, ATX has been speculated to play a role in cancer invasion or metastasis as an autocrine motility factor [6]. However, the exact pathophysiological significance of ATX remained unknown until the discovery of its lysoPLD activity [7,8]. ATX is responsible for the hydrolysis of lysophospholipids (mainly lysophosphatidylcholine), producing LPA in blood (Fig. 1). In heterozygous ATX-null mice, LPA plasma concentration was one-half that in wild-types [9,10]. A strong correlation between serum ATX activity and plasma LPA has also been observed in humans [11] and rats [12]. Homozygous ATX-null mice were embryonically lethal [9]. Collectively, these results suggest that the pathophysiologic functions of ATX can largely be attributed to its ability to produce LPA.

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doi:10.1016/j.cca.2012.07.014

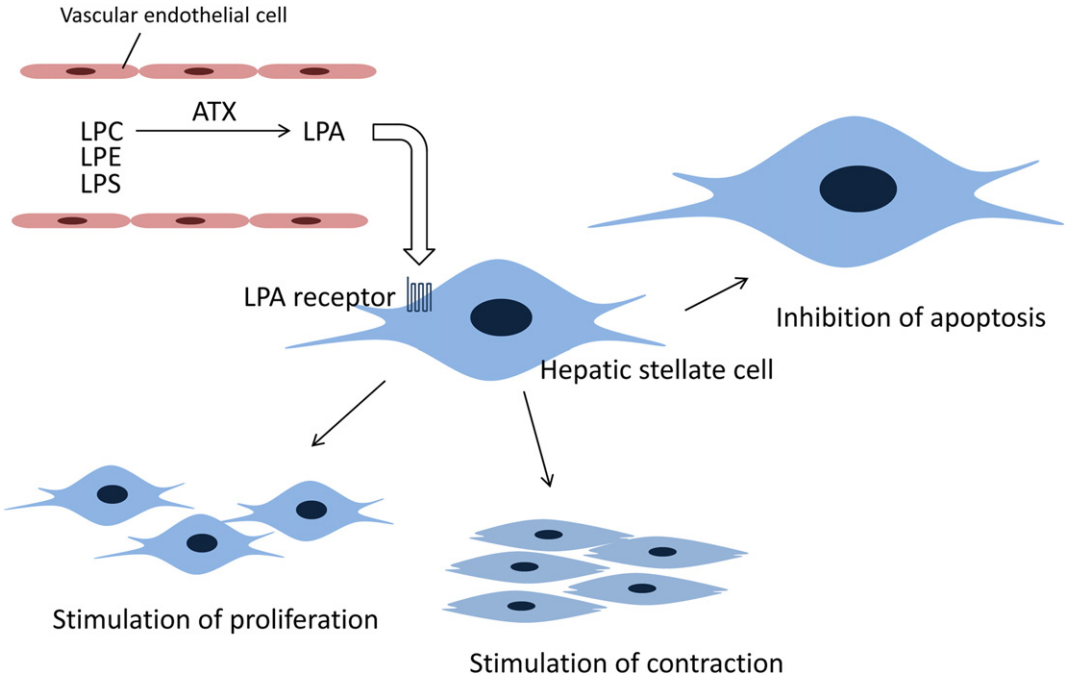

Fig. 1. Major productive pathway for LPA in the blood and its effects on hepatic stellate cells *in vitro*. Plasma LPA is mainly produced from lysophosphatidylcholine (LPC), lysophosphatidylethanolamine (LPE), and lysophosphatidylserine (LPS) by ATX. LPC, LPE and LPS can originate from the membrane phospholipids of activated platelets, and LPC can also be produced from phosphatidylcholine by lecithin-cholesterol acyltransferase. LPA stimulates the proliferation and contraction of hepatic stellate cells and inhibits the apoptosis of these cells *in vitro*, suggesting that LPA may be pro-fibrogenic in the liver.

2. LPA stimulates hepatic stellate cell proliferation and contraction and inhibits apoptosis

Irrespective of cellular insult, ie, viral infection, alcohol or drug abuse, a wound healing response generally occurs in injured liver tissue. The persistence of this response may result in liver fibrosis. Among liver cells, hepatic stellate cells are known to play a major role in the fibrotic process in which they undergo a phenotypic change to myofibroblasts [13–15]. This activation ultimately results in proliferation, production of abundant extracellular matrices, increased contractility and motility. The process of liver fibrosis now appears to be reversible in rats [16] and humans [17], and hepatic stellate cell apoptosis may be a key event in this reversal, since the mechanisms responsible for the spontaneous resolution of rat liver fibrosis involve hepatic stellate cell apoptosis [18,19], and the direct induction of hepatic stellate cell apoptosis has reduced experimental liver fibrosis in rats [20]. Thus, many factors with potentially fibrogenic activities in the liver have been evaluated in light of their effects on hepatic stellate cell activation and apoptosis [15].

Regarding its potential effect on hepatic stellate cells, LPA was first shown to stimulate rat hepatic stellate cell proliferation in a pertussis toxin-sensitive manner, suggesting that LPA could be a pro-fibrogenic factor in liver [21]. Because hepatic stellate cells reside around the hepatic sinusoid, a unique vasculature in liver, the contraction of these cells results in increased pressure in the hepatic sinusoid and hence the portal vein. Thus, hepatic stellate cells appear to play a direct role in pathogenesis of portal hypertension, a major complication associated with liver fibrosis. In this context, LPA was further shown to enhance the contractility of hepatic stellate cells *in vitro* through Rho/Rho kinase activation [22,23], suggesting that LPA might be involved in the pathogenesis of portal hypertension. Furthermore, LPA was shown to inhibit hepatic stellate cell apoptosis *in vitro* through Rho/Rho kinase activation [24]. Collectively, these *in vitro* findings suggest that LPA may be a pro-fibrogenic factor in the liver (Fig. 2).

3. Increased blood ATX and LPA in liver fibrosis

Although previous *in vitro* findings have suggested a link between LPA and liver fibrosis *in vivo*, whether LPA plays a primary role in the pathogenesis of liver fibrosis has remained uncertain. No phenotypic changes in livers of LPA receptor-deficient mice have been demonstrated [25]. No modulations in liver fibrosis have so far been reported in these mice after liver injury. Of note, previous evidence has demonstrated relatively low gene expression of LPA receptors in liver [26], suggesting that the roles of LPA may be limited in liver fibrosis. In contrast, LPA receptor-deficient mice were markedly protected from bleomycin-induced pulmonary fibrosis [27].

However, experiments to clarify the significance of ATX and LPA in liver fibrosis found plasma LPA and serum ATX activity increased in patients with chronic hepatitis C. A strong correlation was observed between plasma LPA and serum ATX activity. Furthermore, plasma LPA and serum ATX activity were correlated with blood markers for liver fibrosis, such as serum hyaluronate and platelet counts [11]. Plasma LPA and serum ATX activity increased in association with liver fibrosis stage histologically in these patients. An association between liver fibrosis and plasma LPA and serum ATX activity has been further confirmed in experimental rat models [12]. In this study, plasma LPA and serum ATX activity were correlated to the extent of liver fibrosis induced by carbon tetrachloride [12].

What mechanism responsible for increased plasma LPA and serum ATX activity in liver fibrosis? Factors involved with increasing serum ATX activity are likely primary because plasma LPA is essentially regulated by ATX [11,12]. To explain increased serum ATX activity, two possibilities should be considered (although the origin and fate of serum ATX have not been fully elucidated): increased ATX production as a result of liver fibrosis or reduction in ATX clearance. In carbon tetrachloride-induced fibrotic rat livers, ATX mRNA expression was unaltered [12], ie, production was not increased. Increased serum ATX activity was observed in 70% hepatectomized rats as early as