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Articles

Apolipoprotein(a) Attenuates Endogenous Fibrinolysis in the Rabbit Jugular Vein Thrombosis Model In Vivo

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► Abstract

Background In many case-control as well as epidemiological studies, increased lipoprotein(a) [Lp(a)] levels are considered to constitute an independent risk factor for premature coronary artery and cerebrovascular disease. Lp(a) resembles an LDL particle with an additional linked protein [apolipoprotein(a), apo(a)], whose molecular structure has been

demonstrated to be homologous to the fibrinolytic proenzyme plasminogen. Because of the high similarity between plasminogen and apo(a), apo(a) may potentially interfere in the fibrinolytic system by competing with plasminogen for fibrin binding sites. In vitro studies have demonstrated that Lp(a) indeed competes with plasminogen binding to fibrin and inhibits tissue plasminogen activator (TPA)-mediated activation of plasminogen. No direct in vivo studies to test this hypothesis have been performed.

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Methods and Results To test this hypothesis, we studied the effect of a recombinant form of apo(a) on endogenous and TPA-mediated thrombolysis in an in vivo model of experimental venous thrombosis. Thrombi containing either 16 µg r-apo(a), 8 µg r-apo(a), or vehicle (HEPES-buffered saline, control) were formed in the jugular veins of a rabbit and showed significantly reduced endogenous thrombolysis after 60 minutes in a dose-dependent fashion, ID $2.7 \pm 0.9\%$ and $4.6 \pm 1.8\%$, respectively, versus $7.4 \pm 1.6\%$ of that of the control. High concentrations of incorporated apo(a) significantly reduced TPA-induced thrombolysis ($12.2 \pm 2.5\%$ versus $22.2 \pm 2.6\%$ in the control thrombi), but no effect of lower concentrations of incorporated r-apo(a) was demonstrated on the exogenous TPA-induced thrombolysis.

Conclusions The present study demonstrates the attenuation of endogenous fibrinolysis by apo(a) in an in vivo model of experimental venous thrombosis, lending support to the proposed mechanism of impaired fibrinolysis by which Lp(a) may contribute to atherothrombotic disorders.

Key Words: plasminogen activators • fibrinolysis • thrombolysis • plasminogen • apolipoproteins

► Introduction

Numerous case-control and prospective studies have shown that Lp(a) is an independent risk factor for premature coronary artery and cerebrovascular disease.^{1 2 3} Marked inherited variability exists in human plasma Lp(a) levels, with concentrations of <1 mg/dL to >100 mg/dL. Approximately 25% of the population possesses Lp(a) levels greater than the apparent threshold of 25 mg/dL, which more than doubles their risk of developing coronary heart disease. However, little is known about how Lp(a) concentrations are regulated and how Lp(a) exerts its pathogenic effects.

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The Lp(a) particle closely resembles LDL both in lipid composition and in the presence of apo B-100. Lp(a) is distinguishable from LDL by the presence of an additional protein moiety designated apo(a), which is covalently linked to apo B-100 and most likely gives rise to the unique structure and functional properties attributed to Lp(a). It has been shown that the linkage of apo(a) and apo B-100 to form Lp(a) particles occurs extracellularly in plasma.⁴

Apo(a) is a large plasma glycoprotein (28% carbohydrate by weight⁵), and by comparative DNA analysis, extensive homology has been demonstrated between apo(a) and the fibrinolytic proenzyme plasminogen.⁶ Apo(a) contains multiple tandem repeats of a sequence closely resembling plasminogen kringle IV, which has an important role in the binding of plasminogen to fibrin.⁷ Different-size apo(a) isoforms have been described with molecular masses ranging from 300 to 700 kD, depending on the number of kringle IV repeats.⁸ The kringle IV sequences are followed by sequences corresponding to the kringle V and protease regions of plasminogen. However, because of a critical substitution of arginine with serine at the equivalent activator site, the apo(a) molecule is resistant to cleavage by plasminogen activators.⁶ It has been hypothesized that the high degree of structural similarity between apo(a) and plasminogen may lead to interference of apo(a) with the activation of plasminogen.

This, in turn, may result in an overall antifibrinolytic effect that could help to explain the atherothrombotic effects of elevated levels of Lp(a) in vivo. In this context, it has been shown in vitro that Lp(a) can compete with plasminogen for substrates such as fibrinogen and fibrin⁹¹⁰ and also for the binding of plasminogen to receptors present on endothelial cells⁷¹¹ and platelets.¹² Binding to each of these substrates is mediated by lysine affinity sites present in the kringle domains of apo(a) and plasminogen. Such effects, however, have not yet been established in vivo.

Observations in transgenic mice expressing human apo(a) revealed a reduction in r-TPA-induced lysis of pulmonary emboli, indicating the relevance of the effect of apo(a) on fibrinolysis in vivo.¹³

Recently, r-apo(a)¹⁴ was generated, containing 17 kringle IV repeats as well as the kringle V and protease domains. This r-apo(a) was found to inhibit TPA-mediated plasminogen activation as well as the degradation of fibrin by plasmin in vitro.¹⁵ Furthermore, it was shown by an in vitro association assay that the 17-kringle r-apo(a) associates covalently with rabbit LDL to form Lp(a) complexes.¹⁶ On the basis of these findings, we designed a study of the effect of r-apo(a) on endogenous and TPA-induced thrombolysis in an in vivo model of experimental venous thrombosis in the rabbit.

► Methods

Production and Purification of r-Apo(a)

The expression, purification, and characterization of r-apo(a) has been described previously.¹⁴ Briefly, r-apo(a) consisting of 17 kringle IV-like domains as well as the kringle V and protease-like domain was assembled from the apo(a) cDNA clones reported previously.⁶ The apo(a) cDNA bounded by *Eco*RI sites was ligated into the pRK5 expression vector containing the cytomegalovirus promoter. Human embryonic kidney (239) cells were transfected by the method of calcium phosphate coprecipitation.¹⁷ Positive clones were identified by immunoperoxidase staining with an apo(a) monoclonal antibody (2G7), and apo(a) production was measured by ELISA.¹⁸

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Apo(a) was purified from roller bottle conditioned medium. Harvested media (2 L) were concentrated 10-fold by ultrafiltration; concentrated media were treated with PMSF (1 mmol/L in ethanol), precipitated with 45% ammonium sulfate, and resuspended in 10 mL of 20 mmol/L HEPES (pH 7.4)/150 mmol/L NaCl (HBS) and chromatographed over Biogel 1.5 mmol/L (Sigma). r-Apo(a)-containing fractions were pooled and passed over a lysine-sepharose 4B column. The column was washed with 20 mmol/L HEPES (pH 7.4)/0.5 mol/L NaCl, and bound r-apo(a) was eluted with 20 mmol/L HEPES (pH 7.4)/1.0 mol/L NaCl/200 mmol/L ϵ -aminocaproic acid; eluted r-apo(a) was dialyzed at 4°C against HBS, analyzed by SDS-PAGE, and stored at -70°C.

Measurement of Endogenous and TPA-Mediated Thrombolysis

Experimental Preparation

New Zealand White rabbits of $\approx$ 2.5 kg were anesthetized with 9 mg ketamine (Aecoket) and 0.5 mL rompun 2% (Bayer) IM. Anesthesia was maintained by the repeated administration of

ketamine. The carotid artery and jugular veins were exposed by a median incision in the neck. The carotid artery was cleared, and a cannula (baby feeding tube, 1.6-mm diameter) was introduced for the administration of anesthetics. The jugular veins were cleared on both sides for a distance of 2 cm, and all side branches were ligated. The venous segments were isolated by application of vessel clamps proximally and distally.

To assess the extent of thrombolysis, radiolabeled thrombi were injected into the isolated venous segments. The decrease in the initial radioactivity of the preformed thrombi reflected the extent of thrombolysis. Therefore, homologous citrated rabbit blood was mixed with ^{125}I -labeled fibrinogen (Amersham; final radioactivity, 10 $\mu\text{Ci/mL}$). An aliquot of 150 μL of this mixture was aspirated in a syringe containing 25 μL human thrombin (human thrombin T7009, Sigma Chemical Co; 150 U/mL), 45 μL CaCl_2 (0.25 mol/L), and 80 μL r-apo(a) (0.20 mg/mL or 0.10 mg/mL diluted in HBS) or 80 μL HBS (control) and quickly injected into the isolated venous segment. The same procedure was repeated for the contralateral side. After 30 minutes of aging, the vessel clamps were removed and blood flow was restored. Thrombolysis was assessed by comparison of the remaining radioactivity of the thrombi at the end of the experiment with the initial radioactivity of the preformed clots. Thrombolysis was expressed as a percentage of the initial thrombus volume (300 μL).

Study Design

To assess the dose effect of apo(a) on the extent of endogenous thrombolysis, the rabbits received clots containing either (1) 8 μg r-apo(a) diluted in 80 μL HBS [corresponding to 6.7 mg/dL plasma Lp(a)], (2) 16 μg r-apo(a) diluted in 80 μL HBS [corresponding to 13.3 mg/dL plasma Lp(a)], (3) 32 μg r-apo(a) diluted in 80 μL HBS [corresponding to 26.6 mg/dL plasma Lp(a)], (4) 64 μg r-apo(a) diluted in 80 μL HBS [corresponding to 53.2 mg/dL plasma Lp(a)], or (5) 80 μL HBS alone (vehicle, control). Each group consisted of eight thrombi.

To assess the effect of apo(a) on TPA-mediated thrombolysis, an additional series of rabbits was assigned to receive either incorporated r-apo(a) [16 μg ; final concentration Lp(a), 13.3 mg/dL; or 64 μg ; final concentration Lp(a), 26.6 mg/dL] in combination with 0.25 mg/kg r-TPA IV (Actilyse, Boehringer Ingelheim) or vehicle (HBS) incorporated in the clot in an equal volume in combination with intravenous r-TPA. Each group consisted of eight thrombi. The r-TPA was administered as a bolus injection immediately after the vessel clamps were removed and the blood flow was restored. The effect on thrombolysis was assessed after 60 minutes, at which time the thrombi were counted blindly by a second investigator.

Statistical Analysis

Statistical analysis was performed by ANOVA and Newman-Keuls test. A value of $P < .05$ was considered statistically significant. All values are presented as mean $\pm$ SD.

Ethical Considerations

All animal studies were approved by the Institutional Review Board for Animal Experiments and were performed according to the guidelines of the American Physiological Society and Dutch Law for Animal Experiments.

► Results

The incorporation of apo(a) significantly attenuated the endogenous thrombolysis compared with the control thrombi. In control animals, an endogenous thrombolysis of $7.4 \pm 1.6\%$ in 60 minutes was observed. However, incorporation of apo(a) into the thrombi resulted in a dose-dependent reduction of endogenous thrombolysis (Fig 1). The incorporation of increasing doses of r-apo(a) in the clots [ranging from 8 to 64 μg , corresponding to Lp(a) plasma concentrations of 6.7 to 53.2 mg/dL] resulted in a significantly reduced endogenous thrombolysis, up to a 5.2-fold inhibition of thrombolysis of thrombi containing 64 μg apo(a) (thrombolysis, $1.4 \pm 0.8\%$; $P < .001$ compared with controls). Also, incorporation of lower concentrations of apo(a) in the clots resulted in impaired thrombolysis: $4.6 \pm 1.8\%$ in thrombi containing 8 μg r-apo(a) ($P < .05$ compared with controls), $2.7 \pm 0.9\%$ in thrombi containing 16 μg r-apo(a) ($P < .01$ compared with controls), and $2.2 \pm 1.1\%$ in thrombi containing 32 μg r-apo(a) ($P < .01$ compared with controls).

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Figure 1. Endogenous thrombolysis of thrombi formed in rabbit jugular veins. Extent of thrombolysis, containing either increasing concentrations of apo(a) (range, 8 to 64 $\mu\text{g}/200 \mu\text{L}$) or vehicle [0 μg apo(a)], was measured after 60 minutes. Thrombolysis is expressed as percentage of initial thrombus volume. Values are mean $\pm$ SD. * $P < .05$, ** $P < .01$, *** $P < .001$.

In the animals receiving thrombolytic treatment (0.25 mg/kg TPA), no difference in the efficacy of the TPA-induced thrombolysis was observed between the clots containing a concentration of 16 μg r-apo(a) versus the control clots, but higher concentrations of apo(a) significantly reduced TPA-induced thrombolysis (Fig 2). The administration of 0.25 mg/kg TPA induced a lysis of $22.2 \pm 2.6\%$ of the clots containing 16 μg apo(a) versus $21.9 \pm 3.0\%$ lysis in the control clots ($P = .72$). However, in thrombi containing much higher concentrations of apo(a) (64 $\mu\text{g}/\text{clot}$), TPA-induced thrombolysis was significantly reduced to $12.2 \pm 2.5\%$ ($P < .01$ compared with control thrombi).

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Figure 2. Exogenous r-TPA-induced thrombolysis of thrombi formed in rabbit jugular veins. Extent of thrombolysis, containing either apo(a) at a concentration of 16 or 64 $\mu\text{g}/200 \mu\text{L}$ or vehicle [HBS, 0 μg apo(a)], was measured after 60 minutes. Thrombolysis is expressed as percentage of initial thrombus volume. Values are mean $\pm$ SD. * $P < .01$.

► Discussion

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Many studies have implicated elevated Lp(a) in the pathogenesis of atherosclerosis. Specifically, elevated Lp(a) levels have been associated with the extent of coronary artery and cerebrovascular disease, myocardial infarction, and vascular graft stenosis.^{1 2 3 19} However, the mechanism by which an elevated Lp(a) level exerts its atherosclerotic effect has not been clarified. Lp(a) is preferentially absorbed via the scavenger receptor and is a ligand with a relatively low affinity for the LDL receptor compared with LDL itself,²⁰ providing a possible mechanism for premature atherosclerosis by the formation of foam cells.²¹ This hypothesis is consistent with the observed unresponsiveness of elevated Lp(a) plasma levels to HMG-CoA reductase inhibitors and the additive effect of increased LDL levels on the development of atherosclerosis in patients with elevated Lp(a) plasma levels.^{21 22} However, the extensive homology of the molecular structure of Lp(a) to plasminogen is intriguing.⁶ Because of the high degree of similarity between the apo(a) part of Lp(a) and plasminogen, elevated Lp(a) levels have been suggested to interfere with plasminogen function, resulting in an overall antifibrinolytic effect that might explain the atherothrombotic effect of elevated Lp(a) levels. In the present study, incorporation of apo(a) significantly attenuated endogenous clot lysis in a dose-dependent fashion, demonstrating the inhibitory effect of apo(a) on the fibrinolytic system.

Interestingly, our findings were similar to the results of a recent in vitro study in which the effect of the same r-apo(a) was studied in a plasma-based clot lysis assay.¹⁵ In that study, the incorporation of 0.14 and 0.27 $\mu\text{mol/L}$ r-apo(a) resulted in a clot lysis time prolongation of 29% and 64%, respectively, whereas in our study the incorporation of 8 μg (0.11 $\mu\text{mol/L}$) and 16 μg (0.21 $\mu\text{mol/L}$) r-apo(a) resulted in a reduction in endogenous thrombolysis of 28% and 69%, respectively. In addition, in our study, clots containing even higher concentrations of apo(a) showed a further inhibition of endogenous thrombolysis. In contrast to the diminished endogenous thrombolysis of the apo(a)-containing clots, no effect on clot lysis induced by exogenously administered TPA was observed in our study when the thrombi contained 16 μg r-apo(a). Apparently, the local inhibitory effect of apo(a) was overcome by the exogenous TPA administered. However, when clots were formed containing fourfold higher concentrations of Lp(a), TPA-induced thrombolysis was significantly impaired. These results are in agreement with recent observations in transgenic mice expressing the human apo(a) gene,¹³ although the clinical significance of these findings has not yet been established.²³

Several mechanisms by which apo(a) may interfere in the process of fibrinolysis have been suggested. In the presence of fibrin, plasminogen activation is facilitated by the initial formation of a binary complex between fibrin and TPA, which subsequently forms a ternary complex with plasminogen, resulting in the generation of plasmin. Kinetic studies have shown an enhanced catalytic efficiency of TPA-induced plasminogen activation in the presence of fibrin.²⁴ Lp(a) has demonstrated competition with plasminogen for lysine-binding sites present on fibrin.^{9 10} Therefore, Lp(a) may interfere in the activation of plasminogen by displacement of plasminogen from the TPA/fibrin complex or by inhibition of the formation of the initial TPA/fibrin complex by a direct interaction with TPA.²⁵ Many groups have described an inhibitory effect of Lp(a) on plasminogen binding to fibrin and cellular receptors, resulting in reduced in vitro clot lysis,^{3 10 11 12 15 26} although not all investigators could

confirm these results.^{27 28 29} Although it has been shown that the recombinant apo(a) used in our study binds to rabbit LDL,¹⁶ we cannot be sure whether the observed effects are due to formed Lp(a) particles or to free apo(a). However, previous reports suggest that the interference of Lp(a) with the fibrinolytic system is dependent on the apo(a) moiety of the molecule, because apo(a) is the pivotal determinant of Lp(a) binding to fibrinogen and inhibition of fibrinolysis.

The present in vivo results lend support to the concept that elevated Lp(a) levels do attenuate fibrinolysis on a local level. Another mechanism by which Lp(a) may exert its prothrombotic effect is attenuation of the activation of TGF- β by the inhibition of plasmin formation at the surface of endothelial cells. TGF- β has been shown to play an important role in the inhibition of smooth muscle cell migration and proliferation and is activated by local plasmin generation.^{30 31} These observations indicate that the inhibition of plasmin generation by Lp(a) not only may result in a reduced resolution of fibrin depositions, as demonstrated in our study, but in fact also may induce smooth muscle cell migration and proliferation.

In conclusion, in the present study the in vivo attenuation of endogenous thrombolysis by apo(a) was demonstrated, indicating that one mechanism by which Lp(a) exerts its effect on coronary and cerebrovascular disease is mediated by an impaired fibrinolytic process. Although a good correlation has been shown between the results obtained in the rabbit jugular vein thrombosis model and animal models of arterial thrombosis, it should be realized that additional studies in humans are necessary to further elucidate the role of Lp(a) in atherothrombotic disease.

► Selected Abbreviations and Acronyms

apo	= apolipoprotein
HBS	= HEPES-buffered saline
Lp(a)	= lipoprotein(a)
r-apo(a)	= recombinant apo(a)
r-TPA	= recombinant TPA
TGF- β	= transforming growth factor- β
TPA	= tissue plasminogen activator

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