Apolipoprotein(a) Enhances Platelet Responses to the Thrombin Receptor–Activating Peptide SFLLRN

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Abstract—Elevated levels of lipoprotein(a) [Lp(a)] are correlated with an increased risk of atherosclerotic disease. We examined the effect of recombinant apolipoprotein(a) [r-apo(a)] and Lp(a) on responses of washed human platelets, prelabeled in the dense granules with [14C]serotonin and suspended in Tyrode’s solution, to ADP and the thrombin receptor–activating peptide SFLLRN. No effect of the 17 kringle (K), 12K, or 6K r-apo(a) derivatives (at concentrations of 0.35 and 0.7 μmol/L) or Lp(a) (up to 0.1 μmol/L) on primary ADP-induced platelet aggregation was observed. In contrast, weak platelet responses stimulated by 7.5 μmol/L SFLLRN were significantly enhanced by the r-apo(a) derivatives; eg, 0.7 μmol/L 17K r-apo(a) increased aggregation from 15±4% to 58±6%, release of [14C]serotonin from 9±3% to 36±6%, and formation of thromboxane A2, measured as its stable metabolite thromboxane B2, from 7±1 to 29±5 ng/10⁹ platelets (n=3; P<0.04 to 0.015). Significant enhancement of aggregation and release of granule contents was observed at a concentration of 17K r-apo(a) as low as 0.175 μmol/L. Purified Lp(a) (0.25 to 0.1 μmol/L) also enhanced SFLLRN-induced aggregation and release in a dose-dependent manner. Although plasminogen (0.7 and 1.5 μmol/L) and low density lipoprotein (0.025 to 0.1 μmol/L) both exhibited potentiating effects on SFLLRN-mediated platelet aggregation, the magnitude of the responses was less than that observed with either the r-apo(a) derivatives or Lp(a). The enhanced responses of platelets via the protease-activated receptor-1 thrombin receptor in the presence of Lp(a) may contribute to the increased risk of thromboembolic complications of atherosclerosis associated with this lipoprotein. (Arterioscler Thromb Vasc Biol. 1998;18:1393-1399.)

Key Words: lipoprotein(a) ■ apolipoprotein(a) ■ platelet function ■ thrombin receptor–activating peptide ■ SFLLRN

Elevated plasma levels of Lp(a) (ie, >20 to 30 mg/dL) have been identified as a significant risk factor for coronary artery disease, myocardial infarction, and infarcted artery patency.¹ ² However, the mechanisms by which Lp(a) mediates its pathogenic effects are poorly understood and may involve prothrombotic or proatherogenic roles.¹ ³ Structurally, Lp(a) is very similar to LDL but is distinguished by the unique protein moiety apo(a), which is attached to apoB-100 by a single disulfide bridge.⁴ ⁵ The primary sequence of apo(a) shares extensive homology with the serine protease zymogen plasminogen and contains multiply repeated copies of a sequence that closely resembles plasminogen kringle IV, followed by sequences exhibiting a high degree of similarity to the kringle V and protease domains of plasminogen.⁶ Ten distinct classes of kringle IV sequences in apo(a) are present in all individuals; the kringle IV type 2 motif (also known as the major repeat kringle) is present in variable numbers (<10 to >40) and constitutes the molecular basis of Lp(a) isofrom size heterogeneity.⁷ ⁸ Of the kringle IV sequences in apo(a), kringle IV type 10 most closely resembles that of plasminogen kringle IV. Like plasminogen kringle IV, apo(a) kringle IV type 10 also has lysine-binding properties⁹ and has been postulated to mediate the interaction of Lp(a) with lysine residues present in such biological substrates as fibrin.¹⁰ ¹¹ ¹² The similarity between apo(a) and plasminogen has been interpreted as suggesting a potential prothrombotic/antifibrinolytic effect for Lp(a) that may underlie thromboembolic complications associated with elevated Lp(a) levels in vivo. Several studies have demonstrated that Lp(a) can compete with plasminogen for binding to fibrin surfaces¹⁰ ¹¹ and that both Lp(a)¹¹ and apo(a)¹³ inhibit plasminogen activation mediated by tissue plasminogen activator. It has also been demonstrated that Lp(a) binds to isolated platelets via a lysine-dependent interaction¹⁴; there are conflicting reports as to whether the glycoprotein (GP) IIb-IIIa complex is involved in Lp(a) binding to platelets.¹⁴ ¹⁵ It was recently shown that...
Lp(a) inhibits collagen-induced platelet aggregation,\textsuperscript{16,17} perhaps by inhibition of platelet adhesion to collagen.\textsuperscript{16} Because LDL is generally considered to be proaggregatory with respect to platelets,\textsuperscript{16,19} these results suggest a role for the apo(a) component of Lp(a) in influencing platelet interactions.

In the current study, we examined the effect of recombinant apo(a) [r-apo(a)] derivatives differing in the number of kringle IV type 2 motifs on platelet responses (aggregation, secretion of granule contents, and formation of thromboxane A\textsubscript{2} [TXA\textsubscript{2}]) mediated by ADP or the thrombin receptor–activating hexapeptide SFLLRN, 2 agonists that stimulate secretion of granule contents, and TX formation stimulated by SFLLRN. Our results clearly demonstrate that even though primary ADP-induced aggregation of platelets is not affected by the r-apo(a) species or isolated Lp(a), they significantly enhance aggregation, secretion of granule contents, and TX formation stimulated by SFLLRN. This enhancement is not affected by the number of kringle IV type 2 motifs in the r-apo(a) protein. These data illuminate a novel mechanism by which Lp(a) may contribute to thromboembolic complications associated with atherosclerosis.

**Methods**

**Construction of Apo(a) Expression Plasmids**

The 17 kringle (K), 12K, and 6K r-apo(a) derivatives used in this study are shown in Figure 1A; they differ in number of identically repeated kringle IV type 2 domains (8, 3, and 0, respectively). Details of the construction of the corresponding expression plasmids are described elsewhere.\textsuperscript{21} All constructs were assembled in the pRK5 expression vector, which contains the cytomegalovirus promoter and simian virus 40 termination sequences.\textsuperscript{22}

**Generation of Stably Expressing Cell Lines**

Human embryonic kidney (293) cells\textsuperscript{23} (American Type Culture Collection, Rockville, Md) were cultured in 100-mm dishes in the presence of minimal essential medium (Gibco-BRL) supplemented with 5% FCS. Cell lines stably expressing the various r-apo(a) derivatives were generated by cotransfection of 293 cells with 10 \( \mu \)g of the respective expression plasmid and 1 \( \mu \)g of a plasmid encoding the neomycin resistance gene \( \alpha \) per culture dish by calcium phosphate coprecipitation.\textsuperscript{21} Transfectants were selected by culturing the cells in the presence of 800 \( \mu \)g/mL of the antibiotic G418 (Gibco-BRL) as previously described.\textsuperscript{21} Clones stably expressing the apo(a) derivatives were identified by ELISA.\textsuperscript{21}

**Protein Purification**

Transfected 293 cells stably expressing the various r-apo(a) derivatives were cultured in roller bottles containing 250 mL of OptiMEM (Gibco-BRL) for 72 hours. Conditioned medium was harvested, clarified by brief centrifugation, and loaded onto a 50-mL lysis-Sepharose CL-4B (Pharmacia) column. The column was washed with PBS containing 0.5 mol/L NaCl, and protein was eluted with 0.2 mol/L \( \epsilon \)-aminocaproic acid in this buffer. Protein-containing fractions were pooled, dialyzed at 4°C against HEPES-buffered saline (HBS; 20 mmol/L HEPES, pH 7.4, containing 150 mmol/L NaCl), precipitated with 50% \( (\text{NH}_4)_2\text{SO}_4 \), and pelleted by centrifugation at 12 000 \( g \) for 20 minutes at 4°C. The resulting pellet was dissolved in HBS and dialyzed against the same buffer. The protein concentration was determined by measuring absorbance at 280 nm. Extinction coefficients for each r-apo(a) protein were determined by tyrosine difference spectra.

Glu-plasminogen was purified from fresh frozen plasma by adsorption to lysine-Sepharose CL-4B, followed by elution with \( \epsilon \)-aminocaproic acid.\textsuperscript{27} The dialyzed sample was precipitated with 70% (\( \text{NH}_4 \))\textsubscript{2}SO\textsubscript{4}, and the precipitate was recovered by centrifugation, dissolved in HBS, and dialyzed against HBS. Plasminogen ran as a single band of 92 kDa on a 4% to 20% SDS–polyacrylamide gel electrophoresis gel under reducing conditions. This preparation had no activity toward the plasmin-specific chromogenic substrate S-2251 (Kabi).

**Lipoprotein Purification**

To isolate Lp(a) from human plasma, blood samples were obtained from a fasting donor with high Lp(a) levels and an apo(a) isoform containing 19 kringle IV type 2 repeats, as obtained from a fasting donor with high Lp(a) levels and an apo(a) isoform containing 19 kringle IV type 2 repeats, as described previously.\textsuperscript{30} The lipoprotein fraction was isolated from a 1.08:1.21 density gradient ultracentrifugation, followed by gel filtration chromatography as previously described.\textsuperscript{20} Purity of isolated Lp(a) was assessed by agarose gel electrophoresis, and the molar protein concentration of Lp(a) was determined by measuring absorbance at 280 nm.

![Figure 1. A. Composition of r-apo(a) species used. Top line, Organization of the 17K r-apo(a), which was derived from the published cDNA sequence as previously described.\textsuperscript{22} The organization of the 12K and 6K r-apo(a) derivatives is shown relative to the 17K species. In all cases, unfilled boxes designate kringle repeats of identical amino acid sequence (ie, kringle IV type 2); hatched boxes represent \( \epsilon \)-aminocaproic acid substitutions relative to the major kringle repeat. The 10 types of kringle IV sequences are indicated above the 17K derivative. Shaded boxes represent the kringle V sequence, and black bars correspond to the apo(a) protease-like domain (P). The position of the free cysteine in apo(a) kringle IV type 9 is shown with a bar. The 12K and 6K constructs contain a hybrid kringle (diagonal line), which represents a fusion of kringle IV type 1 with either kringle IV type 2 (for the 12K derivative) or kringle IV type 5 (for the 6K species). The small black rectangle at the left end of each construct represents the signal sequence. B, SDS-PAGE analysis of purified r-apo(a) derivatives. r-apo(a) was purified by lysine-Sepharose affinity chromatography from conditioned medium harvested from 293 cells stably expressing each derivative. The indicated recombinant proteins (5 to 10 \( \mu \)g) were analyzed by SDS-PAGE under nonreducing conditions using a 4% to 20% polyacrylamide gradient gel stained with Coomassie blue.](image-url)
concentration was determined by a double monoclonal antibody-based ELISA insensitive to apo(a) size heterogeneity. Addition-
ally, the purified Lp(a) was determined to be free of contaminat-
ing plasminogen by immunoblotting (data not shown).

LDL within the 1.006<d<1.05 g/mL density range was isolated from human plasma by sequential flotation. In brief, plasma (containing 1 mmol/L PMSF, 1 mmol/L EDTA, and 0.02% NaN3) was centrifuged at 436,000 x g for 2 hours at 15°C. The d<1.006 g/mL fraction was removed, and the infranatant density was adjusted to <1.05 g/mL with NaBr and centrifuged for 2 more hours. At this time, the d<1.05 g/mL fraction was isolated and centrifuged at a density of 1.05 g/mL for another 2 hours. LDL isolated from this centrifugation step was found to be devoid of contaminating Lp(a), as determined by both immunoblotting and ELISA (data not shown). Lp(a) and LDL preparations were dialyzed extensively against HBS before they were used in platelet studies.

Preparation of Platelets

Suspensions of washed platelets were prepared from human donors who had not taken medication affecting platelet function for at least 2 weeks before the blood donation. (Informed consent was obtained from each subject, and experiments were approved by the University of Toronto Human Subjects Review Commit-
tee.) Blood (60 to 80 mL) was anticoagulated with the acid-
citrate-dextrose solution of Aster and Jandl32 (88.4 mmol/L trisodium citrate, 71.4 mmol/L citric acid, and 111 mmol/L dextrose), using 1 part solution to 6 parts blood. The following preparation was performed at 37°C. Blood was centrifuged at 190g for 15 minutes to obtain the supernatant platelet-rich plasma. Platelet-rich plasma was centrifuged at 2500g for 15 minutes to obtain a platelet pellet. The pellet was gently resuspended in 10 mL of a washing solution based on Tyrode’s solution (137 mmol/L NaCl, 2.7 mmol/L KCl, 11.9 mmol/L NaHCO3, 0.42 mmol/L NaH2PO4, 1 mmol/L MgCl2, 2 mmol/L CaCl2, and 5.5 mmol/L glucose) containing heparin (50 U/mL). Platelet dense granules with [14C]serotonin, 0.1 mCi/mL, pH 7.35. To label the platelet dense granules with [14C]serotonin, 0.1 μCi/mL of 5-hydroxy-3-indolyl[1-14C]ethyl-2-amine/creatinine sulfate (55 mCi/mmol, Amersham) was incubated with this suspension for at least 15 minutes. The platelet pellet was recovered by centrifu-
gation at 12000g for 10 minutes, and the platelets were resus-
uspended in the second washing solution, which was the same as the first but without heparin. The platelets were resuspended in 50 mL of Tyrode-albumin solution, pH 7.35, in an aggregometer for up to 5 minutes, they did not stimulate aggregation stimulated by 4×104 platelets/mL fibrinogen. Values are mean±SEM (n=3).

Measurement of Secretion of Granule Contents and TX Formation

Three minutes after addition of ADP or 5 minutes after addition of SFLLRN, supernatant samples were prepared by centrifugation of the stirred platelet suspensions for 1 minute at 12,000 g in an Eppendorf centrifuge. These samples were used to determine the percentage of [14C]serotonin secreted from the prelabeled platelets and the formation of TXB2, the stable metabolite of TXA2, by radioimmunoassay (NEK-007, NEN Canada).

Statistical Analyses

Values are reported as mean±SEM with the number of experiments indicated. Paired t tests (with adjustment for multiple tests when necessary) were used to analyze differences between controls and treated samples. Differences were considered statistically significant at P<0.05.

Results

Expression and Purification of r-apo(a) Derivatives

The r-apo(a) derivatives shown in Figure 1A were expressed in 293 (human embryonic kidney) cells. Proteins were puri-
fied to homogeneity from conditioned medium harvested from stably expressing cell lines by lysine-Sepharose affinity chromatography. Purified proteins (5 to 10 μg) were analyzed by SDS-PAGE under nonreducing conditions, followed by Coomassie blue staining (Figure 1B); details of the analysis are given in the legend of Figure 1.

Platelet Function Studies

Neither the r-apo(a) derivatives, plasminogen, Lp(a), nor LDL, on their own, resulted in detectable platelet activation. Several concentrations of each substance were tested; the highest concentrations were 0.7 μmol/L r-apo(a) derivatives, 1.5 μmol/L plasminogen, 0.1 μmol/L Lp(a), and 0.3 μmol/L LDL. When stirred with suspensions of washed platelets in an aggregometer for up to 5 minutes, they did not stimulate platelet aggregation, nor did they stimulate secretion.
of [14C]serotonin from prelabeled platelets over background levels (data not shown).

ADP-Induced Aggregation

Suspensions of washed platelets were stimulated with ADP in the absence or presence of the r-apo(a) derivatives shown in Figure 1A. In accord with our earlier observations,38,39 ADP stimulated only a primary phase of aggregation; secretion of [14C]serotonin was negligible. This primary, ADP-induced aggregation was not affected by the different r-apo(a) species. Several concentrations were tested, the highest being 0.7 μmol/L (Figure 2). Plasminogen, Lp(a), and LDL also had no effect on ADP-induced aggregation. Several concentrations of each substance were tested, the highest being 1.5 μmol/L plasminogen, 0.1 μmol/L Lp(a), and 0.3 μmol/L LDL (data not shown).

SFLLRN-Induced Responses

SFLLRN corresponds to the new amino terminus of the moderate-affinity thrombin receptor, protease-activated receptor-1 (PAR-1) after cleavage by thrombin; a synthetic peptide of this sequence stimulates platelet aggregation, secretion of granule contents, and formation of TXA2.40–44 The concentration of SFLLRN (7.5 μmol/L) was chosen because, by itself, it caused considerably less than maximum aggregation and secretion of [14C]serotonin, making it possible to demonstrate whether enhancement or inhibition of these platelet responses occurred in the presence of the substances under investigation. Aggregation and secretion of [14C]serotonin stimulated by 7.5 μmol/L SFLLRN were significantly enhanced by 0.7 μmol/L 17K r-apo(a) (Figure 3A and 3B); TXB2 (an index of TXA2 formation) was also significantly increased (from 6.8±1.4 to 29.0±4.7 ng/10^9 platelets, n=3, P<0.025). A lower concentration (0.35 μmol/L) of the 17K r-apo(a) also enhanced SFLLRN-induced responses (Figure 3A and B). Decreasing the number of kringle IV type 2 motifs in the r-apo(a) did not affect the enhanced responses to SFLLRN (Figure 3A and B). The lowest concentration of r-apo(a) that significantly enhanced SFLLRN-induced platelet aggregation was 0.175 μmol/L, with aggregation being increased from 14.6±7.1% to 30.8±7.3% and secretion of [14C]serotonin from 9.2±3.8% to 18.3±5.2% by 17K r-apo(a) (n=3; P<0.0025 and 0.025, respectively). Plasminogen, at concentrations of 0.7 and 1.5 μmol/L, also enhanced SFLLRN-induced aggregation and secre-

![Figure 3](http://atvb.ahajournals.org/)

**Figure 3.** Enhancement by r-apo(a) species (0.35 or 0.7 μmol/L) differing in the number of kringle IV type 2 domains of (A) platelet aggregation and (B) secretion of [14C]serotonin stimulated by 7.5 μmol/L SFLLRN. Values are mean±SEM (n=3). *P<0.04 to 0.0075 (A) and <0.04 to 0.015 (B) compared with control.

![Figure 4](http://atvb.ahajournals.org/)

**Figure 4.** Enhancement by plasminogen (plgn) and the 12K r-apo(a) derivative of platelet responses stimulated by 7.5 μmol/L SFLLRN. Addition of SFLLRN is indicated by the arrow; the percentage of [14C]serotonin secretion from prelabeled platelets is given in the boxes beside the aggregation curves. L.T. indicates light transmission. Data are representative of 2 experiments with similar results.

![Figure 5](http://atvb.ahajournals.org/)

**Figure 5.** Effects of purified Lp(a) (V, v) and LDL (Œ, Œ) on aggregation (V, Œ) and secretion of [14C]serotonin (V, Œ) when platelets were stimulated by 7.5 μmol/L SFLLRN. Data, expressed as percentages, are representative of 2 experiments with similar results.
tion, but not to the same extent as r-apo(a) (Figure 4). The combination of plasminogen (1.5 μmol/L) with 17K r-apo(a) (0.35 or 0.7 μmol/L) had an effect similar to that of 17K r-apo(a) alone. Lp(a) (0.025 to 0.1 μmol/L) greatly enhanced SFLLRN-induced aggregation and secretion of [14C]serotonin in a dose-dependent manner, and LDL (in the same concentration range) had a slight enhancing effect (Figure 5).

**Discussion**

Although a number of case-control and prospective studies have demonstrated a correlation between elevated Lp(a) levels and atherosclerosis,1,2 the mechanisms underlying these observations remain unclear. Few studies have examined the effect of Lp(a) on platelet function, which may play a key role in the atherosclerotic process by enhancing intravascular thrombosis. We examined the effect of both Lp(a) and the unique protein component apo(a) on platelet aggregation induced by ADP and the thrombin receptor–activating peptide SFLLRN.

Our results show that plasminogen (up to 1.5 μmol/L), Lp(a) (up to 0.1 μmol/L), and LDL (up to 0.3 μmol/L) had no effect on the primary phase of aggregation stimulated by ADP; secretion of [14C]serotonin was negligible in all cases. Additionally, the r-apo(a) derivatives 6K, 12K, and 17K (containing various numbers of the major repeat kringle sequence; see Figure 1A) had no effect on this process when protein concentrations up to 0.7 μmol/L were used. This is in keeping with the results of Gries et al,16 who reported that Lp(a) had no significant effect on (maximum) aggregation induced by ADP. However, Pedreno et al17 reported that Lp(a) inhibited ADP-induced aggregation and that LDL enhanced it. The differences in these results may be related to the source of lipoprotein and methods used for lipoprotein purification.

In contrast with our results showing a lack of effect on ADP-induced aggregation, we observed enhancement of SFLLRN-induced platelet aggregation and concomitant secretion of granule contents in the presence of the 6K, 12K, and 17K r-apo(a) derivatives (at concentrations of 0.35 and 0.7 μmol/L for each r-apo(a) species); the Lp(a) particle (at concentrations of 0.025 to 0.1 μmol/L) also enhanced SFLLRN-induced responses in a dose-dependent manner. Given that LDL had only a slight enhancing effect (Figure 5), our data suggest that the potentiating effect of Lp(a) on SFLLRN-induced platelet responses is mediated by the apo(a) component of the Lp(a) particle. This is supported by the recent observation of Pedreno et al17 that LDL interacts with platelets through a different receptor than Lp(a), which may bind to platelets primarily via GP IIb of the GP IIb-IIIa complex.15 A potentiating effect of plasminogen on SFLLRN-induced aggregation was also observed; however, the enhancement of aggregation with the use of 0.7 μmol/L plasminogen was <50% of that observed using an equimolar concentration of the 12K r-apo(a) derivative (see Figure 4). As such, it appears that a major proportion of the observed potentiating effect of apo(a) on platelet aggregation arises as a result of the unique properties of apo(a) rather than those properties of the protein that are shared with plasminogen.

We recently showed that plasminogen binds to r-apo(a) or Lp(a) in solution, with $K_s$ values of ≈20 and 6 nmol/L, respectively.45 The complexes bind poorly to plasminogen-binding sites on fibrin. Accordingly, we investigated the effect of plasminogen on the r-apo(a)–mediated enhancement of platelet responses to SFLLRN. The effect of plasminogen and r-apo(a) in complex was identical to the effects of r-apo(a) alone, indicating that at their approximate physiological concentrations, plasminogen does not significantly influence the ability of r-apo(a) to enhance platelet responses to SFLLRN.

It is interesting to note that the effects of r-apo(a) on stimulated platelets are specific and contrasting with respect to mechanisms of action. For example, primary ADP-induced aggregation, which is not influenced by r-apo(a), does not involve the activation of intracellular phospholipase C,16 whereas SFLLRN-induced responses, which are enhanced by both r-apo(a) and Lp(a), involve activation of phospholipase C, leading to hydrolysis of phosphatidylinositol 4,5-bisphosphate.57,48 Stimulation of platelets with thrombin also activates phospholipase C, and Gries et al16 reported that maximal platelet aggregation stimulated by 0.1 U/mL thrombin was not affected by Lp(a). However, it is not possible to observe an enhancement of a response that is already maximal. Thrombin induces minimal to maximal aggregation responses over a very narrow range of concentrations; thus, in the current study, SFLLRN, which does not have as steep a dose-response curve as thrombin, was used at a concentration that consistently stimulated weak platelet responses.

The concentrations of r-apo(a) derivatives used in our study (0.35 and 0.7 μmol/L) are physiologically relevant and correspond to plasma Lp(a) concentrations of ≈30 and 60 mg/dL for the 17K derivative, respectively; 30 mg/dL Lp(a) is above an apparent coronary risk threshold for Lp(a), which was defined on the basis of extensive epidemiological data.1,2 The in vivo significance of the enhancement of SFLLRN-induced platelet responses by apo(a)/Lp(a) remains to be elucidated. However, it is possible that the potentiating effect of Lp(a) on platelet aggregation at the site of thrombus formation in vivo may contribute to thromboembolic complications associated with atherosclerosis. The proaggregatory effects of other proatherogenic lipoproteins (VLDL and LDL) on platelet function have been previously reported16,19,20,25. LDL has been shown to potentiate collagen-mediated platelet aggregation.16

We did not observe an effect of the number of kringle IV type 2 sequences on the magnitude of the potentiating effect of r-apo(a) on SFLLRN-mediated platelet responses. This suggests that in vivo, apo(a)/Lp(a) isoform size heterogeneity may not play a significant role in this process. In general, the significance of Lp(a) isoform size heterogeneity in the pathophysiological role of this lipoprotein remains undetermined, although Wild et al20 recently reported an increased frequency of small apo(a) isoforms in men with myocardial infarction or coronary death in a case-control study. However, few Lp(a)-substrate interactions identified and characterized to date are dependent on apo(a) isoform size,2 although there are several reports that apo(a) isoform size affects the binding of Lp(a) to
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fibrin and affects the extent to which Lp(a) inhibits fibrinolysis in vitro.51,52

In summary, we demonstrated, for the first time, that the apo(a) component of Lp(a) potentiates SFLLRN-stimulated platelet responses in vitro. These observations suggest a novel mechanism by which Lp(a) may contribute to the thromboembolic complications of atherosclerosis.

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