Chylomicron-Induced Prothrombin Activation and Platelet Aggregation

Ning Xu, Ann-Kristin Öhlin, Åke Nilsson

Abstract The effects on platelet aggregation of native rat chyle chylomicrons, chylomicron remnants, and chylomicrons that had been preincubated with rat or human EDTA-plasma, serum, whole blood, or pure human prothrombin were examined. The native chyle chylomicrons did not induce platelet aggregation but decreased ADP- and thrombin-induced platelet aggregation and \(^{14}C\)serotonin release. Chylomicron remnants also failed to induce platelet aggregation, but they potentiated the aggregation and the \(^{14}C\)serotonin release induced by ADP and thrombin. Aggregation, after a lag phase of 15 to 20 minutes, was seen when platelets were incubated with chylomicrons that had been preincubated with plasma and then isolated as the top layer after a single centrifugation at \(d=1.006\). This aggregation was inhibited in a dose-dependent manner by an antisera against prothrombin that also inhibited thrombin-induced platelet aggregation. After washing by centrifugation the plasma-preincubated chylomicrons did not induce platelet aggregation, but this effect could be restored by adding a small amount of prothrombin, which did not cause aggregation when added alone or together with native chyle chylomicrons. Addition of 2% (vol/vol) plasma, however, induced aggregation when added together with either native chyle chylomicrons or washed preincubated chylomicrons, but not when added alone. Binding of \(^{125}I\)-labeled prothrombin to native chyle chylomicrons was demonstrated by gradient ultracentrifugation. During incubation of washed plasma-preincubated chylomicrons with \(^{125}I\)-prothrombin and platelets, a significant conversion of \(^{125}I\)-prothrombin to \(^{125}I\)-thrombin occurred, as demonstrated by autoradiography after separation on sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The interaction between chylomicrons and prothrombin, and possibly other coagulation proteins, thus enhances prothrombin activation in the presence of platelets. (Arterioscler Thromb. 1994;14:1014-1020.)

Key Words • platelets • lipoproteins • prothrombin

The state of activation of platelets may be influenced by interaction with circulating lipoproteins. Activated platelets, ie, platelets more responsive to stimulation, may have an enhancing role in the atherosclerotic process. Low-density lipoproteins (LDLs) enhance platelet reactivity to agonists in vitro, whereas high-density lipoproteins (HDLs) have opposite effects. Patients with type IV hyperlipidemia who have increased levels of plasma very-low-density lipoproteins (VLDLs) exhibit enhanced platelet activity, whereas the platelets of patients with type V hyperlipoproteinemia who have exceedingly high levels of plasma triglycerides, mainly as chylomicrons, appear less responsive. Platelet chylomicrons from type V patients decreased thrombin- and ADP-induced aggregation and \(^{14}C\)serotonin release in normal platelets. In patients with type III hyperlipoproteinemia, in which chylomicron remnants accumulate in plasma, the platelets exhibit a shortened survival, increased turnover, and enhanced aggregation and release reactions. Also in the IIb phenotype, in which the concentration of both cholesterol and triglycerides is raised, the platelets exhibit enhanced aggregation and release reactions. It is generally assumed that chylomicrons are not associated with extensive atherogenesis, whereas chylomicron remnants may be very atherogenic. Hyperlipidemia and hypercoagulability were recently the subjects of an extensive review article.

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In another study (N.X., Å.N., 1993, unpublished data) focused on the uptake of \[^{3}H\]arachidonic acid (20:4)–labeled chylomicrons and chylomicron remnants by rat platelets, we found that chylomicrons that had been preincubated with plasma induced platelet aggregation, thereby making meaningful studies of the uptake of these particles impossible. Other studies have shown that prothrombin and factor Xa may bind to VLDL, partially through a Ca\(^{2+}\)-dependent association. In terms of hypercoagulability, VLDL might thus serve as an alternative localized site for activation of prothrombin or other coagulation enzymes. Other data suggest that the proteolytic processing by coagulation enzymes of apolipoprotein (apo) E and apoB of VLDL might change the receptor by which these lipoproteins are removed in such a way that foam cell formation is promoted. In vitro, only the VLDL of all plasma lipoprotein classes supported the conversion of prothrombin to thrombin by factor Xa.

In this study we examine the effects of native chyle chylomicrons and chylomicron remnants on rat platelet aggregation and demonstrate that native chyle chylomicrons exposed to plasma in vitro may enhance prothrombin activation and cause rat platelet aggregation.

Methods

Preparation of Native Chyle Chylomicrons and Chylomicron Remnants

To characterize the partitioning of 20:4 in different lipid classes in native and preincubated chylomicrons and in chylomicron remnants, chylomicrons labeled with \[^{3}H\]20:4 were used in some experiments. Fifty micromoles of \[^{3}H\]20:4 (100.0 Ci/mol, [5,6,8,9,11,12,14,15-\[^{3}H\]aryl]arachidonic acid, NET-298), 25 mg of cholesterol (Kebo Laboratories), and 1 mg egg phosphatidylcholine (Sigma), both dissolved in 1 mL of chlo-
rof, were mixed, blown to dryness with nitrogen, and immediately dispersed in 1 mL of hot 154 mmol/L NaCl by buzzing. The dispersion was then mixed with 2 mL of 20% (wt/vol) Intralipid (Kabi Vitrum AB). In other experiments rats were infused with the same amount of Intralipid without radioactive fatty acids to prepare unlabeled native chylomicrons. The mesenteric lymph duct of male white Sprague-Dawley rats that had been fasted for 24 hours (weight 250 to 280 g) was cannulated, and a gastric fistula was inserted. Twenty-four hours after surgery, 3 mL of the radioactive emulsion or Intralipid was infused through the gastric fistula during 1 hour. The chyle was collected for 6 hours on ice in the presence of Na2EDTA (final concentration, 2 mmol/L). Native chyle chylomicrons were floated by ultracentrifugation at 25,000 rpm for 2 hours at 4°C using a Beckman SW 40 Ti swinging-bucket rotor after the chyle was adjusted to d=1.063, layered under 188 mmol/L NaCl solution containing 1 mmol/L Na2EDTA. Chylomicron remnants were prepared by injecting native chyle chylomicrons into eviscerated rats (weight 2 mL of chyle). The ability to induce platelet aggregation was different. There was less or no effect of preincubated chylomicrons on platelet aggregation when the proportions of plasma were 33% and 50%. When 1 mL of chylomicrons (10 mg triacylglycerol per milliliter) was injected through the right jugular vein. The blood was collected by aortic puncture after 30 minutes; 2 mL of ACD solution (containing 2.2 g trisodium citrate, 0.8 g citric acid, and 2.45 g dextrose in 100 mL of distilled water) was used as the anticoagulant. After the blood cells were removed by centrifugation at 3000 g for 30 minutes, the plasma was adjusted to d=1.063, layered under 188 mmol/L NaCl solution containing 1 mmol/L Na2EDTA, and then ultracentrifuged at 32,000 rpm for 18 hours at 4°C using a Beckman SW 40 Ti rotor. Under these conditions the main part of the remnants formed from chylomicrons, but only small amounts of remnants from endogenous VLDL were recovered. Triacylglycerol content of chylomicrons was determined by an enzymatic kit method (Triglycerides GPO-PAP, Boehringer Mannheim Test Combination).

Procedures for Preincubation of Native Chylomicrons

When chylomicrons (10 mg triacylglycerol per milliliter) were incubated with different proportions of plasma (33%, 50%, 67%, and 75%; vol/vol) for 30 minutes, the ability to induce platelet aggregation was different. There was less or no effect of preincubated chylomicrons on platelet aggregation when the proportions of plasma were 33% and 50%. When 1 mL of chylomicrons (10 mg triacylglycerol per milliliter) was incubated with 2 mL of plasma for 5, 10, 15, 30, and 60 minutes, the incubation time also influenced the ability of preincubated chylomicrons to stimulate platelet aggregation.

There was less or no effect of preincubated chylomicrons on platelet aggregation after preincubation for 5 or 10 minutes. There were no obvious changes in platelet aggregation if the incubation time was 60 minutes instead of 30 minutes. As a standard procedure 1 mL chylomicrons containing 10 mg triacylglycerol was therefore preincubated with 2 mL plasma or serum or 2.68 mL of Tyrode's buffer A (control) or native chyle chylomicrons at submaximal concentrations of thrombin (0.2 U/mL) and ADP (5 μmol/L). In one series of experiments the effects of the lipoproteins on the ADP- and thrombin-induced platelet aggregation were examined, 40 μL of the lipoproteins and 10 μL of the ADP or thrombin solution were added. Concentrations of ADP and thrombin are shown in the legends to the tables and figures. The aggregation was continuously monitored by measurement of the change in light transmission, using a two-channel recorder (Rec-2, Pharmacia Fine Chemicals). The ability of each individual platelet preparation to respond to aggregatory stimuli was tested by adding submaximal concentrations of thrombin (0.2 U/mL) and ADP (5 μmol/L). In some studies the effects of rabbit anti-human prothrombin antiserum (gift from Professor Johan Stenflo, Department of Clinical Chemistry, Malmö General Hospital, Sweden) on the aggregation induced by chylomicrons that had been preincubated with plasma or prothrombin were examined.

Platelet [14C]Serotonin Release

Platelet [14C] serotonin release was studied according to Aviram et al.20 Twenty milliliters of PRP was incubated with 4 μCi [14C] serotonin (50.7 mCi/mmol, NEC-225) at 37°C for 30 minutes during gentle shaking. The incubation mixture was then centrifuged at 1500g for 20 minutes, and the platelet pellet was washed once with Tyrode's buffer B and resuspended in 20 mL of Tyrode's buffer A. Next, 450 μL of [14C] serotonin-labeled platelet suspension was incubated with 40 μL of Tyrode's buffer A (control) or native chyle chylomicrons or chylomicron remnants at 37°C for 10 minutes with stirring (250 rpm), and then 10 μL of ADP (5 μmol/L) or thrombin (0.2 U/mL) was added as a stimulus for 5 minutes. At the end of the stimulation, 0.2 mL of 100 mmol/L Na2EDTA was added to prevent reuptake of free [14C] serotonin by the platelets. The samples were immediately removed to plastic tubes on ice and centrifuged at 12,000 rpm for 1 minute using a Microfuge (Beckman). We removed 200 μL supernatant to scintillation vials containing 10 mL of toluene/Instagel (1:1, vol/vol) and counted radioactivity in a scintillation counter (TRI-CARB 460 CD Liquid Scintillation System).
Studies of Binding and Activation of Prothrombin

Highly purified human prothrombin (DIA-Service) was iodinated with ¹²⁵I by the chloramine T method. The specific radioactivity of iodinated prothrombin was 400 to 600 cmpg/mg prothrombin. Fifty microliters of ¹²⁵I-prothrombin (≈1.25 µg) was incubated with 1 mL of native chyle chylomicrons (10 mg triacylglycerol) for 30 minutes at 37°C in ultracentrifuge tubes. After incubation, 1 mL of a stock solution of NaBr-NaCl (1.006); the density of chylomicrons was always included. The percent release of prothrombin. Fifty microliters of ¹²⁵I-prothrombin (≈1.25 µg) was added to an incubation mixture with platelets and lipoproteins performed at 37°C for 20 minutes in the aggregometer as described above. The platelets were pelleted at 12,000 rpm for 1 minute, and the supernatant was delipidated with ethanol/ether (3:1 [vol/vol]) at 4°C for 24 hours. The protein precipitate was resolubilized in 50 mmol/L tris(hydroxymethyl)aminomethane-acetic acid buffer (pH 7.5) in the presence of 35 mmol/L sodium dodecyl sulfate (SDS) and separated by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) (Excel Gel SDS, gradient 8-18, Pharmacia). Pepsin (34.7 kD) and bovine serum albumin (66 kD) (Sigma) were used as molecular weight standards. Changes in the partitioning of ¹²⁵I between prothrombin (≈70 kD), prethrombin 2 (37 kD), and thrombin (33 kD) were demonstrated by autoradiography of the gels.

Distribution of [³H]Arachidonic Acid in Native Chyle Chylomicrons, Preincubated Chylomicrons, and Chylomicron Remnants

Lipids in native chyle chylomicrons, preincubated chylomicrons, and chylomicron remnants were extracted by chloroform/methanol (1:1, vol/vol). Lipid classes were separated by thin-layer chromatography on silica gel G plates that were developed in light petroleum ether/diethyl ether/methanol/acetic acid (80:20:2.25:1 [vol/vol/vol/vol]). Cholesteryl ester, triacylglycerols, 1,3- and 1,2-diacylglycerols, monoacylglycerols, and phospholipids were identified by staining with iodine vapor and scraped into counting vials. One milliliter methanol/water (1:1 [vol/vol]) and 9 mL Instagel/toluene (1:1 [vol/vol]) were added, and radioactivity was then determined in a Packard Tri Carb 460 CD liquid scintillation system. Quenching was determined by the automatic external standard.

Statistical Analysis

Values are reported as mean±SD. Data were assessed by ANOVA with contrasts. A value of P<.05 was considered significant.

Results

Distribution of [³H]Arachidonic Acid in Lipid Classes in Native Chyle Chylomicrons, Preincubated Chylomicrons, and Chylomicron Remnants

Data are given in Table 1. There were only small differences in the proportion of tritium that was found in the free fatty acid fraction between native and preincubated chylomicrons and chylomicron remnants. The 1,2-diglyceride radioactivity was slightly higher in the chylomicrons that had been preincubated with rat plasma (1.8%) than in the native chyle chylomicrons (1.0%). The chylomicron remnants contained 7.3% of the tritium in the 1,2-diglyceride. There was a decrease in phospholipid radioactivity in the preincubated chylomicrons and chylomicron remnants, in agreement with the observation that phospholipids are transferred from chylomicrons to HDL during the exposure to plasma. There was a 20-fold increase in the proportion of tritium in cholesteryl ester in remnants compared with native chyle chylomicrons, indicating that an extensive hydrolysis of triacylglycerol had occurred. SDS-PAGE of apolipoproteins also indicated that the expected changes, ie, a decrease in apoA-I and apoA-IV and an increase in apoE, had occurred (data not shown).

Effect of Native Chyle Chylomicrons and Chylomicron Remnants on Rat Platelet Aggregation and [¹⁴C]Serotonin Release

As shown in Table 2, the native chyle chylomicrons inhibited rat platelet aggregation that was induced by ADP or thrombin compared with controls. Chylomicron remnants had contrasting effects: they enhanced ADP-induced rat platelet aggregation but did not enhance thrombin-induced platelet aggregation. In addition, platelet [¹⁴C]serotonin release was affected differently by native chyle chylomicrons and chylomicron remnants.
The chylomicron remnants increased the [14C]serotonin release induced by ADP and thrombin, whereas the results with native chyle chylomicrons present did not differ significantly from those in controls (Table 2).

Effects of Native Chyle Chylomicrons and Preincubated Chylomicrons on Rat Platelet Aggregation

Chylomicrons that had been preincubated with rat EDTA-plasma or whole blood or with human EDTA-plasma and then isolated by a single flotation induced aggregation of rat platelets after a 15- to 20-minute lag period, whereas an equal volume of the infranatant had no effect. No measurable aggregation was observed when platelets were incubated with an equivalent amount of native chyle chylomicrons or with the chylomicrons that had been preincubated with rat or human serum (Fig 1). When antiserum against human prothrombin was added to the rat platelet suspension before the addition of the chylomicrons that had been preincubated with rat or human plasma, platelet aggregation was inhibited by the antiserum in a dose-dependent fashion (Fig 2). In the same experimental setup, control serum (normal rabbit serum) and human albumin did not influence platelet aggregation (data not shown). When native chyle chylomicrons had been preincubated with human prothrombin and isolated by a single flotation, they induced platelet aggregation after a lag phase, whereas an equal volume of the infranatant did not. This aggregation could also be inhibited by addition of the antiserum against prothrombin in a dose-dependent manner (Fig 3). The antiserum also inhibited platelet aggregation induced by thrombin (data not shown). If the chylomicrons that had been preincubated with plasma were washed by repeated ultracentrifugation in isotonic saline containing 1 mmol/L Na₂EDTA, they did not induce platelet aggregation. If a small amount of prothrombin (125 ng), which did not induce platelet aggregation by itself, was added to incubations with the washed preincubated chylomicrons, platelet aggregation occurred. When this amount of prothrombin was added to incubations with native chyle chylomicrons, no aggregation was seen. Both washed preincubated chylomicrons and native chyle chylomicrons induced rat platelet aggregation when added together with 2% (vol/vol) rat plasma (Fig 4). With much larger amounts of prothrombin (>1.5 µg), aggregation could also be induced with native chyle chylomicrons and with prothrombin alone.

Table 2. Effect of Native Chyle Chylomicrons and Chylomicron Remnants on Washed Platelet Aggregation and [14C]Serotonin Release

<table>
<thead>
<tr>
<th></th>
<th>Aggregation, % (n=9)</th>
<th>[14C]Serotonin Release, % (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADP (5 µmol/L)</td>
<td>Thrombin (0.2 U/mL)</td>
</tr>
<tr>
<td>Control*</td>
<td>44.6±3.1</td>
<td>78.8±6.3</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>32.5±5.4†</td>
<td>56.4±5.2†</td>
</tr>
<tr>
<td>Remnants</td>
<td>66.8±4.7†</td>
<td>80.4±1.3</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*Platelet aggregation was induced by ADP or thrombin in washed platelets with the addition of 40 µL of Tyrode’s buffer A.

1P<.05 vs control experiments. Data are from one of two similar experimental series.

Binding of 125I-Prothrombin to Native Chyle Chylomicrons and Conversion to Thrombin

After native chyle chylomicrons had been incubated with 125I-prothrombin, binding of 125I-prothrombin to native chyle chylomicrons could be demonstrated by ultracentrifugation. When incubating 1.25 µg of prothrombin with 1 mL native chyle chylomicrons containing 10 mg triacylglycerol, 8% to 10% of the 125I-prothrombin was bound to chylomicrons (Fig 5). When the amount of 125I-prothrombin was increased, the percentage of binding to native chyle chylomicrons decreased (Fig 6). Addition of unlabeled prothrombin or plasma decreased the percent binding of labeled prothrombin to native chyle chylomicrons (Fig 7). During incubation of platelets with 125I-prothrombin in the presence of washed chylomicrons that had been preincubated with

![Figure 1](image-url)
plasma or prothrombin, a significant formation of \(^{125}\text{I}\)-prethrombin and \(^{125}\text{I}\)-thrombin could be demonstrated by autoradiography of the gel after SDS-PAGE. The formed products had molecular weights of approximately 37 kD and 33 kD, respectively. In the incubations with platelets alone with \(^{125}\text{I}\)-prothrombin, no detectable formation of radioactive thrombin was shown. During incubation with native chylomicrons in the presence of platelets, the thrombin formation was less than with the washed preincubated chylomicrons (Fig 8). When washed plasma-preincubated chylomicrons were incubated with \(^{125}\text{I}\)-prothrombin without platelets present, no formation of prethrombin and thrombin could be detected by autoradiography after separation on SDS-PAGE (Fig 8). The presence of both platelets and preincubated chylomicrons was thus necessary for significant prothrombin activation to occur.

**Discussion**

Several pieces of evidence obtained in this study indicate that native chyle chylomicrons after exposure to plasma or in the presence of small amounts of plasma may enhance prothrombin activation in the presence of washed platelets and thereby cause platelet aggregation in vitro. The initial observation was that chylomicrons that had been preincubated with rat or human plasma and then isolated as the top layer, after a single ultracentrifugation at \(d=1.006\), caused rat platelet aggregation after a lag phase of 15 to 20 minutes, whereas the
intranant from the ultracentrifugation, native chyle chylomicrons, and chylomicrons that had been preincubated with serum did not. The aggregation could be inhibited in a dose-dependent manner by adding anti-serum toward prothrombin (Fig 2). Furthermore, chylomicrons that had been preincubated with pure human prothrombin and isolated by a single ultracentrifugation induced platelet aggregation after a lag phase, and this aggregation could also be inhibited by the anti-prothrombin antiserum (Fig 3). Although the chylomicrons that had been preincubated with rat plasma contained a slightly increased proportion of its [3H]20:4 as free fatty acids, this difference in 20:4 levels between the different lipoprotein preparations is an unlikely explanation of the proaggregatory effect of the chylomicrons that had been preincubated with plasma. This suggested that other changes in the composition of the chylomicron surface occurring during the preincubation with plasma were important.

Since it has earlier been shown that VLDL from hypertriglyceridemic patients can bind vitamin K-dependent coagulation proteins,15,16 the question was raised whether prothrombin binding to negatively charged phospholipids of the chylomicron surface may occur. Activated platelets express factor V and factor X activities at their plasma membrane, which in combination with Ca2+ and phospholipid form the prothrombinase complex.28 This mechanism might lead to prothrombin activation and thereby to platelet aggregation in our experiments and may be favored by accumulation of prothrombin at the chylomicron surface. Binding of 125I-prothrombin to chylomicrons could actually be demonstrated both in the absence and presence of plasma (Figs 5 and 6), and most of this binding persisted after repeated washing by centrifugation (data not shown). Yet chylomicrons that had been preincubated with plasma and then washed repeatedly by centrifugation did not induce platelet aggregation. However, if a small amount of prothrombin that did not induce aggregation when added alone or together with native chyle chylomicrons was added together with the washed preincubated chylomicrons, aggregation did occur (Fig 4). Furthermore, the conversion of 125I-prothrombin during incubation of platelets with preincubated and washed chylomicrons clearly exceeded that which occurred during the incubation of platelets with native chyle chylomicrons. The data thus indicated that not only prothrombin binding but also other changes in the chylomicron surface composition that occur during the preincubation with plasma favor prothrombin activa-
tion. The data also indicated that platelets are necessary on the activation of chylomicron-bound prothrombin (Fig 8). It is suggested that some factors that bind on the platelet surface contribute to the activation of chylomicron-bound prothrombin.

We did not find evidence for a strong proaggregatory effect of either chyle chylomicrons or chylomicron remnants in the absence of other agonists. The ADP- and thrombin-induced platelet aggregation and $^{[125]}$I-prothrombin nin release were depressed by native chyle chylomicrons but enhanced by chylomicron remnants. However, chylomicron remnants did not induce platelet aggregation by themselves. In the case of native chyle chylomicrons, the findings agree with those of Aviram et al., who used plasma chylomicrons from type V hyperlipidemia patients and found decreased aggregation and release on normal platelets in vitro.

A main conclusion of this study is that chylomicrons may enhance prothrombin activation in the presence of platelets and thereby cause platelet aggregation in vitro, whereas native chyle chylomicrons as such tend to attenuate the agonist-induced aggregation and release reaction. Several factors may contribute to this phenomenon. The finding that the activation of $^{125}$I-prothrombin was much higher during incubation of platelets with chylomicrons that had been exposed to plasma than during incubation of platelets with native chyle chylomicrons suggests that not only prothrombin binding but also binding of other coagulation factors or other changes in chylomicron surface structure that occur during exposure to plasma favor prothrombin activation. The nature of these changes needs further study. At the present stage the physiological relevance of the findings is hard to evaluate. Neither patients with familial lipoprotein lipase deficiency who develop massive hypertriglycerideremia because of accumulation of chylomicrons nor type V hyperlipidemia patients develop early atherosclerosis.29,30 It would be of interest to compare platelets and chylomicrons from these patients with their normal counterparts in the model system used in this study. Such studies might indicate whether the platelets in these patients have a decreased ability to activate prothrombin in cooperation with triacylglycerol-rich lipoproteins. It would also be of interest to examine the effects on prothrombin activation and platelet aggregation of chylomicrons at different stages of lipolysis during exposure to lipoprotein lipase.

Acknowledgments

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