A Normal Inhibitor of the Blood Coagulation Contact Reaction Product

By H. L. Nossel and J. Niemetz

IN THE INITIAL stages of in vitro human blood coagulation, reactions between the Hageman and PTA factors of plasma and a foreign surface lead to the formation of a coagulant activity known variously as activation product,1 activated PTA factor2 or the contact reaction product.3 The term “contact product” will be used in this report. An inhibitor of this contact product present in plasma has been reported by Ratnoff et al.21,12 and Margolis.4 The presence of such an inhibitor was further suggested by the observation that celite eluate preparations of the contact product have relatively stable coagulant activity; this coagulant activity is rapidly destroyed when the eluate is incubated with normal citrated plasma.3 In the present report a method for measuring the activity of this inhibitor is described and some of its physical and chemical properties are delineated and compared with the previous reports.

Materials

Silicone treated glass tubes and pipettes, and polystyrene tubes were used throughout. Glass tubes (7.5 x 0.8 cm. internal diameter) coated with Siliclad* were used once for clotting and discarded. Human venous blood collected through a #20 gauge needle was citrated with 0.1 volume (4 per cent trisodium citrate ·2H₂O) and the plasma separated from cells after centrifugation for 20 minutes at 2000 g. Plasma was adsorbed with aluminum hydroxide gel† as described by Ratnoff et al.² Oxalated plasma was adsorbed for 10 minutes at 37 C. with barium sulphate (100 mg./ml.) or tri-calcium phosphate (20-100 mg./ml.). Celite 512§ was used to make celite exhausted plasma (20 mg./ml.) and celite eluates from normal plasma³ by incubating citrated plasma with celite (20 mg./ml.) for 10 minutes at 37 C. with intermittent mixing. After centrifugation, the supernatant plasma was discarded and the celite was resuspended and washed thrice with distilled water. The contact product was eluted by suspending the celite for 10 minutes at 37 C. in a volume of buffered hypertonic NaCl(pH 7.2, 1.7M) equal to the initial amount of plasma. After centrifugation the supernatant was dialysed overnight against buffered 0.15M NaCl. This eluate could now be stored at −20 C. for 4 weeks without appreciable loss of activity. Some of its properties have been described.¹³ Plasma fractions prepared by ammonium sulphate precipitation⁵ and by Cohn’s[vi] method were

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*Supplied by Clay-Adams and used as a 10 per cent solution in distilled water.
†Vitarine Co., Inc., New York.
§Supplied by Johns-Manville.
¶Kindly supplied by Dr. Robert N. Pennell of the Protein Foundation, Boston, and by the Nutritional Biochemicals Corporation, Cleveland.

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Fig. 1.—Celite eluate dilution curve. The celite eluate shortens the clotting time of an intact plasma. There is a log log relationship between concentration of contact product and clotting time.

Dissolved in buffered NaCl at the following protein concentrations: fraction II (18–36 mg./ml.); III (9–18 mg./ml.); IV (9–18 mg./ml.); IV-1 (1.2–4.8 mg./ml.); IV-4 (8–25 mg./ml.); V (23–48 mg./ml.), and were dialysed against buffered NaCl before being used. Fractions were tested in the presence and absence of citrate and both before and after aluminum hydroxide adsorption. Plasma euglobulins were precipitated by dialysing 5 ml. plasma against 2 liters of distilled water for 12 hours. The dialysed plasma was exposed to carbon dioxide for a few minutes to lower the pH to 5.6, the precipitate sedimented by centrifugation and then redissolved in 4.5 ml. buffered NaCl.

Sodium chloride solution was buffered to a pH of 7.4 (± 0.1) with veronal acetate and HCl (Michaelis) as described by Biggs and MacFarlane. Cephalin was diluted in buffered NaCl to a concentration of 1/100. Calcium chloride was dissolved in distilled water to the required molarity. Epsilon amino caproic acid and crystalline soy bean trypsin inhibitor were dissolved in buffered NaCl. All chemicals were reagent grade.

Centrifugation was carried out at 4 C, as was dialysis (in Visking casings). Starch block electrophoresis was carried out at 4 C, pH 8.6, 200 volts, 25 m.a., for 18 hours.

Coagulation Methods

1. The measurement of contact product activity. Contact product activity was measured as previously described. Celite eluates from normal citrated plasma were used as the source of contact product activity. Dilutions of this celite eluate were added to tubes containing normal noncontact plasma and cephalin, calcium was then added and clotting times recorded. The logarithm of the clotting time is linearly related to the logarithm of the celite eluate (contact product) concentration (fig. 1).

*J. T. Baker Chemical Co., Phillipsburg, N. J.
†Supplied by Nutritional Biochemicals Corporation, Cleveland.
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Table 1.—Method for Demonstrating Inhibitor Activity

<table>
<thead>
<tr>
<th>Stage 1. Incubation Mixture</th>
<th>Stage 2. Clotting Mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equal volumes of celite eluate and test solution (0.3–1 ml.) incubated in a silicone treated tube at 37 C. pH 7.4–7.6</td>
<td>0.1 ml. noncontact normal plasma, 0.1 ml. cephalin warmed to 37 C. for 40 sec., 0.1 ml. incubation mixture, 0.1 ml. CaCl₂ 0.040 M or 0.025M*</td>
</tr>
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</table>

*When the test solution contained citrate 0.040 M. calcium was used in the clotting mixture. When the test solution did not contain citrate, 0.025 M. calcium was used in the clotting mixture.

Table 2.—Demonstration of the Inhibitor of the Contact Product

<table>
<thead>
<tr>
<th>Incubation Time (min.)</th>
<th>Clotting Time (seconds)</th>
<th>Average Clotting Time (seconds)</th>
<th>Per Cent Contact Product (Calculated as in Figure 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>54.8, 56.2</td>
<td>55.5</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>74.6, 74.6</td>
<td>74.6</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>91.1, 93.5</td>
<td>92.3</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>104.0, 104.2</td>
<td>104.1</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>109.0, 110.2</td>
<td>109.6</td>
<td>9</td>
</tr>
<tr>
<td>30</td>
<td>131.4, 128.6</td>
<td>130.0</td>
<td>5</td>
</tr>
</tbody>
</table>

Incubation mixture:
Celite eluate 1 ml.
Alumina adsorbed plasma 1 ml.

Clotting mixture:
0.1 ml. noncontact plasma
0.1 ml. cephalin
Incubated for 40 seconds at 37 C.
0.1 ml. incubation mixture
0.1 ml. CaCl₂ 0.040 M

2. The demonstration of inhibitory activity. A two-stage method was used to demonstrate inhibitory activity (table 1).

Stage 1. Incubation mixture. Equal volumes of celite eluate and test solution were incubated together at 37 C. and pH 7.4 (±0.1). At intervals the incubation mixture was sampled and tested in Stage 2.

Stage 2. Clotting mixture. One-tenth ml. volumes of noncontact normal plasma and cephalin were mixed and warmed to 37 C. for 40 seconds; 0.1 ml. of incubation mixture and 0.1 ml. calcium were added and the clotting time recorded.

RESULTS

Inactivation of the Celite Eluate by Normal Plasma

Incubation of a mixture of celite eluate and citrated plasma leads to progressive inactivation of the coagulant activity of the eluate as evidenced by increased time of clotting in Stage 2 (table 2). The results obtained at various incubation periods of Stage I can be expressed as per cent contact product remaining by the following method: the clotting time of the incubation mixture at zero time is considered to be 100 per cent contact product activity and is plotted on the celite eluate activity curve of that day. The results obtained at different incubation periods may be interpolated from the same activity...
The Quantitation of Inhibitory Activity

When different concentrations of normal plasma were incubated with celite eluates, the eluate was inactivated at a rate that was dependent upon the concentration of the inhibiting plasma (fig. 3), and inhibitory activity could be measured as follows:

1. The time in minutes required for inactivation of 75 per cent of the coagulant activity of the eluate was plotted against the reciprocal of the plasma concentration and the best straight line drawn through the points. A representative set of results is plotted in figure 4. The time required for the test solution to inactivate 75 per cent of the coagulant activity of the eluate was determined and the concentration of normal plasma to which the test solution was equivalent was determined from the same activity curve (fig. 3). Inhibitory activity below 25 per cent of normal plasma could not be measured accurately. Although initial reaction rates are the most reliable for enzyme assays, quantitation of the contact product is less reliable between 100 and
Fig. 3.—Contact product inactivation as a function of concentration of the inhibitor present in normal plasma. Plasma dilutions were made with citrate saline (control) as indicated.

Fig. 4.—Time required for inactivation of 75 per cent of the contact product by different dilutions of normal plasma.

50 per cent than at lower levels; thus the 25 per cent inhibitor level (75 per cent inactivation point) was chosen.

2. The inhibitor could also be measured by considering only the percentage of eluate coagulant activity remaining after 30 minutes incubation. This percentage is related to the concentration of inhibiting plasma and can be plotted as a straight line on double logarithm paper (fig. 5). From figure 5 it
Fig. 5.—Amount of contact product remaining after incubation for 30 minutes with various dilutions of plasma.

It can be seen that the straight line relationship holds only for plasma concentrations above 25 per cent; thus relative inhibitory activity less than 25 per cent cannot be estimated accurately. If only the zero and 30 minute incubation times are used, six samples can be tested together conveniently. The results of 11 replicate tests on samples of the same stored plasma are shown in table 3.

Some Characteristics of the Inhibitory Reaction

Some characteristics of the inhibitor were determined. Variation in ionic strength did not significantly impede the inhibitory reaction. The action of the inhibitor was sensitive to temperature with very little inhibition occurring at 4 C. (fig. 6). The action of the inhibitor was not affected by the presence or absence of citrate. When the inhibitor source contained factor IX and calcium, a clot promoting reaction occurred which masked the action of inhibitor. Epsilon amino caproic acid (0.001-0.1M in the incubation mixture) did not interfere with the action of the inhibitor, whereas soy bean trypsin inhibitor (0.030 mg./ml. in the incubation mixture) did. (fig. 9).

Physical and Chemical Properties of the Inhibitor

Some physical and chemical properties of the inhibitor in plasma are summarized in table 4. The inhibitor was relatively stable on storage at -20 C. Heating plasma to 50 C. for 30 minutes destroyed almost all the inhibitory activity (fig. 7). The inhibitor was relatively stable between pH values of 5 and 9 maintained for 5 hours, but there was considerable loss of activity in pH values of 4 and 10 (fig. 8). The inhibitor was not dialysable. Normal plasma
Table 3.—Results of Tests for Inhibitory Activity of Alumina Adsorbed Pooled Normal Plasma

<table>
<thead>
<tr>
<th>Dilution of Alumina-Adsorbed Plasma in Citrate-Saline</th>
<th>Citrate-Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1</td>
<td>1/2</td>
</tr>
<tr>
<td>7.8</td>
<td>11.5</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>7.8</td>
<td>11.5</td>
</tr>
<tr>
<td>7</td>
<td>12.5</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>7.2</td>
<td>14.5</td>
</tr>
<tr>
<td>9.7</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>6.4</td>
<td>11</td>
</tr>
<tr>
<td>8.6</td>
<td>14</td>
</tr>
<tr>
<td>7.8</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Average 7.4 13 23

Four normal plasma samples were pooled, adsorbed with aluminium hydroxide and stored at −40°C. in 1 ml. aliquots. Repeat tests for inhibitory activity were carried out over 1 month. The figures represent per cent residual contact product activity after 30 minutes incubation.

Adsorbed with aluminum hydroxide, barium sulphate or tricalcium phosphate showed a significant increase in inhibitory activity, possibly due to removal of a component impeding the action of the inhibitor. Inhibitory activity was not reduced in celite exhausted plasma. On ammonium sulphate precipitation most of the inhibitory activity was concentrated in the plasma fraction precipitated between 55 and 65 per cent saturation. On starch block electrophoresis most of the inhibitory activity was found in the alpha globulin region. Inhibitory activity was not found in Cohn fractions II, III, IV₁, IV₄, V or VI, at the above mentioned protein concentrations.

Fig. 6.—Effect of different temperatures upon the inhibitor activity. Note the rapid diminution of the contact product at increasing temperatures.
Inhibitory activity was present in serum and in all normal plasma samples examined. The inhibitor was also present in plasma from patients with deficiency of the Hageman or PTA factors, factor VIII or factor IX, but insufficient data are available for quantitative comparison.

**DISCUSSION**

The results of tests for inhibitory activity were reasonably reproducible except for an occasional set of results which showed some deviation (table 3). The reason(s) for the significant increase in the activity of the inhibitor following aluminum hydroxide is still obscure. Aluminum hydroxide adsorption

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**Table 4.—Summary of the Properties of the Inhibitor**

<table>
<thead>
<tr>
<th>Property</th>
<th>Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heat stability</td>
<td>Destroyed at 56 C. maintained for 30 minutes</td>
</tr>
<tr>
<td>pH stability</td>
<td>Stable between pH 5 and 9</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Not dialysable</td>
</tr>
<tr>
<td>Eucaryal precipitate</td>
<td>Quantitatively recovered in the supernatant</td>
</tr>
<tr>
<td>Adsorption by heavy metal salts</td>
<td>Not adsorbed by aluminium hydroxide, barium sulphate or Ca₃(PO₄)₂</td>
</tr>
<tr>
<td>(NH₄)₂SO₄ precipitation</td>
<td>Most activity precipitated between 55 and 65% saturation</td>
</tr>
<tr>
<td>Celite</td>
<td>Not reduced in “celite exhausted” plasma</td>
</tr>
<tr>
<td>Serum</td>
<td>Present in serum</td>
</tr>
<tr>
<td>Electrophoretic mobility</td>
<td>Alpha globulin</td>
</tr>
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</table>

Occurrence of the Inhibitor

Inhibitory activity was present in serum and in all normal plasma samples examined. The inhibitor was also present in plasma from patients with deficiency of the Hageman or PTA factors, factor VIII or factor IX, but insufficient data are available for quantitative comparison.

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Fig. 8.—Effect of pH on the inhibitor. Note the relative stability between pH 5 and 9.

Fig. 9.—The effect of soy bean trypsin inhibitor on the inhibitor of the contact product. The incubation mixture contained: 0.3 ml. aluminum hydroxide adsorbed plasma or citrate saline, 0.3 ml. citrate saline, 0.2 ml. soy bean trypsin inhibitor or saline, and 0.6 ml. celite eluate. The concentration of soy bean trypsin inhibitor in each completed incubation mixture is shown in the figure. Note the augmented amount of remaining contact product when the concentration of soy bean trypsin inhibitor is increased.
might act by removing a component which impedes the action of the inhibitor. Factor IX was suspected but aluminum hydroxide adsorption increased the inhibitory activity of plasma from a patient with congenital factor IX deficiency. It is also possible that the adsorption causes a change in inhibitor itself. Until the effect of this adsorption is better understood the activity of both adsorbed and unadsorbed plasma must be studied.

The finding that inhibitory activity was not reduced in celite exhausted plasma suggests that the inhibitor is not consumed during inactivation of the contact product. Since soy bean trypsin inhibitor prevents the inhibitory reaction the possibility exists that the inhibitor may be a proteolytic enzyme.

Inhibition of the contact product was first noted by Margolis, who reported that inhibitory activity was not present in that fraction of plasma precipitated between 25 and 45 per cent \((\text{NH}_4)_2\text{SO}_4\) and in plasma heated to 56 C. Ratnoff et al.\(^2\)\(^{11,12}\) in studying the same phenomenon found an inhibitor of activated Hageman and PTA factors to be precipitated between 50 and 70 per cent ammonium sulphate saturation. The inhibitor was present in plasma fractions IV-1 and IV-4 separated by Cohn's method \(^6\), and was not destroyed in plasma heated to 56 C. An enzymatic activity was suggested, and temperature dependence reported. DFP, HgCl, peroxide or EDTA did not inhibit the activity of the inhibitor. The reason for these occasional differences from our results is not clear.

In comparing this inhibitor with other naturally occurring inhibitors of blood coagulation, a number of properties similar to those of antithrombin III are noted. Antithrombin III is precipitated with albumin by \((\text{NH}_4)_2\text{SO}_4\) and migrates with alpha1 and alpha2 fractions on electrophoresis.\(^10\)\(^{13}\) Heating to 56 C. destroys antithrombin III and its activity is lost at pH values above 9.5 and below 6.\(^6\)

Regarding the role of the inhibitor in the clotting process, it remains to be determined whether the inhibitor delays the clotting of whole blood or plasma. It also remains to be determined whether the inhibitor plays a physiologic role in maintaining fluidity of the blood. Whether fluctuation in the level of the inhibitor occurs in response to the presence of contact product in the circulation and whether the inhibitor is important in maintaining hemostasis or preventing thrombosis all remain to be investigated.

**Summary**

A method is described for studying and measuring the activity of a normally occurring inhibitor of the blood coagulation contact reaction product (activated PTA). The inhibitor, stable on storage at \(-20\) C. was inactivated by heating plasma to 56 C. for 30 minutes. The inhibitor was stable between pH 5 and 9. Inhibitory activity was increased by aluminum hydroxide adsorption and not apparently affected by celite exhaustion of plasma. The inhibitor was present in the fraction of plasma precipitated between 55 and 65 per cent ammonium sulphate saturation and migrated with the alpha globulins electrophoretically. The action of the inhibitor was prevented by soy bean trypsin
inhibitor. Inhibitory activity was present in serum and in all normal plasma samples examined as well as in plasma from patients deficient in Hageman factor, PTA factor or factors VIII or IX. The physiologic and pathologic significance of this inhibitor remains to be determined.

**SUMMARIO IN INTERLINGUA**

Es describite un methodo pro studiar e mesurar le activitate de un normalmente occurrente inhibitor del producto del reaction a contacto in le coagulation de sanguine (activate PTA; PTA = Antecedente de Thromboplastina del Plasma). Le inhibitor, que es stabile in preservation a -20 C, eseva inactivate per calefacser le plasma a 56 C durante 30 minutas. Le inhibitor eseva stabile inter pH 5 e 9. Le activitate inhibitori eseva augmentate per adsorption ad hydroxydo de aluminium e non afficite apparentemente per exhaustion de plasma effectuate con Celite 512 (Johns-Manville). Le inhibitor eseva presente in le fraction de plasma precipitate a un saturation ammonio-sulpahtic de inter 55 e 65 pro cento e migrava in le electrophorese con le globulinas a. Le action del inhibitor eseva prevenite per inhibitor de trypsina de soja. Le activitate inhibitori eseva presente in sero e in omne le normal specimens de plasma studiate e etiam in plasma ab patientes con carentia de factor Hageman, de factor PTA, de factor VIII, o de factor IX. Le signification physiologic e pathologic de iste inhibitor remane a determinar.

**ADDENDUM**

If the terminology recently proposed by Macfarlane (1964) gains acceptance, then contact product would be referred to as "product Xla," and a suitable term for the inhibitor might be "anti-Xla."

**REFERENCES**

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