Distribution and Fate of $^{131}$I-Labeled Components of the Fibrinolysin System

By Nathan Back, D.Sc., Julian L. Ambrus, M.D., Ph.D., and Irving B. Mink, B.A.

In the course of assaying the potency of a variety of fibrinolytic enzyme preparations in dogs and monkeys with isotope-labeled fibrin clots, we observed that the fibrinolytic activity disappeared rapidly from the systemic circulation. Dissolution of blood clots was noted to occur long after the disappearance of measurable circulating fibrinolytic activity. These experimental observations were confirmed in extensive clinical studies.

Rapid disappearance of exogenously administered plasmin was ascribed to (a) complexing of the active enzyme with circulating inhibitors, (b) selective adsorption onto fibrin substrates, (c) passive diffusion from the vascular system to tissue compartments, and (d) catabolism and excretion. To help elucidate the question of the distribution and metabolic disposition of plasmin as well as that of the delayed fibrinolytic effect, methods were sought to label the enzyme with radioactive isotopes.

Iodine$^{131}$ was selected as the tracer of choice because it is readily incorporated into protein molecules, the labeled protein behaves metabolically in a manner similar to the unlabeled compound, and the degradation products are excreted, rather than reutilized.

Since a number of plasminogen preparations activated by different activators were used, the metabolism of individual components of the fibrinolysin system was studied. Thus, an opportunity was provided for studying the relative in vivo specificities of the individual components for the fibrin substrate.

Methods

The following proteins were iodinated with iodine$^{131}$; human plasminogen, Varidase (crude streptokinase), purified streptokinase, human urokinase, and human plasminogen following spontaneous activation and activation by streptokinase or urokinase. Ultracentrifugal studies revealed that approximately 75 per cent of the total protein in the human plasminogen preparation used had a sedimentation constant of 4, the value characteristic for plasminogen. By studying the distribution of plasmin with radioisotope labeling of various components before or after activation, the chance of basing conclusions on results due to artifacts was decreased.

Radioiodination of Proteins

The radioiodination technique, schematically presented in figure 1, involved an oxidative process with sodium nitrite. Two mg. of carrier-free radioactive sodium iodide were added to 0.5 ml. of a 0.002 M potassium iodide solution in

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1.0 ml of 1.0 X HCl. Conversion of the iodide to free iodine and exchange with radioactive iodide was accomplished by addition of 0.2 ml of 0.02 M NaNO₃. After neutralization with 1.0 ml 1.0 M NaOH and 5.0 ml of borate buffer, pH 8.0, the iodine solution was added to the protein solution. The iodinated preparation was then passed through an Amberlite ion-exchange resin,* IR-45 (OH-) to remove free, unbound iodide. The efficiency of the resin, determined by dialysis studies, was such that less than 1 per cent of the radioactivity passed through the resin in the free, unbound form.

Prior to the use of the iodinated preparations, the effect of iodination on their activities was determined. Fibrinolytic activity was measured before and after iodination by techniques described previously. The RPMI fibrinolytic unit is defined as that amount of plasmin which in two minutes will completely lyse 0.6 ml of an 0.3 per cent purified human fibrin clot (formed with 1 NIH unit of purified thrombin) at 45 C. and pH 7.4. Streptokinase activity was expressed in Christensen units 11 and urokinase activity in Ploug units. 12 In view of the uncertainty regarding the molecular weights of plasminogen and other proteins of this system, 8,13 iodination results are expressed as atoms of iodine per milligram rather than mole of protein. This method was necessary particularly in the case of labeled plasmin, which was shown to undergo changes of molecular weight following activation resulting in alpha, beta, and gamma plasmins. 9

As seen in table 1, iodination of streptokinase- or urokinase-activated plasmin caused some reduction of fibrinolytic activity. Iodination of the plasminogen molecule inhibited its activation potential. The ability of urokinase or streptokinase to activate plasminogen remained unchanged following the iodination procedure. Except for urokinase, the atoms of iodine per mg of protein did not exceed 7.5 X 10⁻⁴. Assuming a molecular weight of 143,000 for plasminogen 8 and 60,000 for streptokinase, 14 the number of atoms of iodine per molecule of protein did not exceed 0.5.

Injection of Labeled Proteins

The iodinated preparations were infused intravenously into dogs carrying nonradioactive clots in their femoral and jugular veins. Purified human fibrin clots were formed by previously described procedures. 1 One hour after clot formation, semiconstricting ligatures were placed proximal to the clots to prevent the clots from slipping away while permitting blood flow through the vessel in the event of clot lysis. At hourly intervals following intravenous administration of the iodinated proteins, clots were removed, washed in saline, and levels of adsorbed radioactivity determined in a well-type scintillation counter. The clots were incubated in saline at 37 C. for 48 hours and observed for lysis. Blood samples, removed at intervals during a four-hour period after protein injection, were oxalated and plasma radioactivity and fibrinolytic activity levels determined. At the end of the four-hour experimental period, the dogs were exsanguinated, and organ, urine, and bile

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*Amberlite resin, supplied by Rohm and Haas Company, Resinous Products Division, Philadelphia, Pennsylvania.
### Table 1

**Effect of Iodination on In Vitro Activity of Components of the Fibrinolysis System**

<table>
<thead>
<tr>
<th>Component iodinated</th>
<th>Activator</th>
<th>Atoms iodine per mg. x 10^{-4} Before Iodination</th>
<th>Activity, units/mg.* After Iodination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasmin</td>
<td>Streptokinase</td>
<td>7.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Human plasmin</td>
<td>Streptokinase</td>
<td>0.85</td>
<td>5.0</td>
</tr>
<tr>
<td>Human plasminogen</td>
<td>Streptokinase</td>
<td>4.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Streptokinase</td>
<td></td>
<td>2.0</td>
<td>4545</td>
</tr>
<tr>
<td>Human plasmin</td>
<td>Urokinase</td>
<td>4.2</td>
<td>6.0</td>
</tr>
<tr>
<td>Human plasminogen</td>
<td>Urokinase</td>
<td>7.5</td>
<td>6.0</td>
</tr>
<tr>
<td>Urokinase</td>
<td></td>
<td>27.0</td>
<td>4000</td>
</tr>
<tr>
<td>Human plasmin</td>
<td>Spontaneous</td>
<td>4.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Human plasmin</td>
<td>Spontaneous</td>
<td>3.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Human plasmin</td>
<td>Spontaneous</td>
<td>1.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Bovine plasmin</td>
<td>CHCl₃</td>
<td>1.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Plasmin activity in RPMI units (3); Streptokinase activity in Christensen units; Urokinase activity in Ploug units.*

### Results

#### In Vivo Localization Onto Clots

Following rapid administration, plasmin was found to localize specifically on clots to an extent 10 to 100 times greater than that with the activators alone. Table 2 summarizes the data obtained from clots removed one hour after injection of the agents. The results are expressed as per cent of injected activity per 100 Gm. of clot. A relatively high degree of plasmin adsorption onto the clots was obtained regardless of the position of the radioactive tag, i.e., on the plasminogen, the activator, or the fully activated protein. Purified streptokinase and urokinase localized to the same extent as the iodinated albumin control. The impure streptokinase, in the form of Varidase, adsorbed minimally, while I^{131} did not localize at all. Human plasminogen exhibited a degree of localization to clots greater than that of spontaneously activated human or chloroform-activated bovine plasmin. The results, graphically presented in figure 2, indicate the per cent radioactivity adsorbed to 100 Gm. of clot. Clots removed from plasmin-treated animals and incubated at 37 C. in saline exhibited greater than 50 per cent lysis within 24 hours. Many of the clots completely lysed within that time interval. This was in sharp contrast to animals treated with urokinase or streptokinase where no significant lysis was seen.

#### Plasma Clearance Rates

Plasma clearance of radioactivity was measured over a four-hour period. Plasma clearance rates were calculated on the basis of the per cent radioactivity remaining per ml. plasma and plotted on semilogarithmic paper. Representative curves are seen in figures 3, 4, and 5.

Analysis of the clearance curves revealed at least two disappearance rates. Clearance rates of the plasmin preparations were quite similar, whereas clearance rates of streptokinase were somewhat lower than urokinase. Disappearance rates of I^{131} and albumin followed established patterns. Table 3 summarizes the average rates at which these proteins were cleared from the bloodstream. The average biological half-life of the fast process of the various plasmin preparations in the circulation was four minutes. With few exceptions, the plasmin preparations contained over 60 per cent of this rapidly disappearing portion. Fifty per cent of the remaining slower process was cleared in an average time exceeding four hours. Streptokinase, on the other hand, showed a fast process with an average half-life of 18 minutes. The average half-life of the slower process was greater than four hours.
In a series of experiments, the number of circulating plasmin units calculated on the basis of radioactivity was compared to the actual free plasmin units determined by fibrinolytic assay. A graphic representation of such an experiment is seen in figure 6. Determinations were made on plasma samples from a dog which received streptokinase-activated plasmin $^{131}$I. In this experiment, the iodination procedure did not cause any loss of in vitro fibrinolytic activity. A progressive decrease in plasmin activity, based on the radioactive counts, can be seen. Actual plasmin activity, based on fibrinolytic assays, indicates a rapid disappearance of fibrinolytic activity. Within one-half hour after plasmin injection, no assayable level of activity was detected. At that time, activity based on circulating radioactivity amounted to over 30 units per 100 ml. of plasma.

### Tissue Distribution

Data on the tissue distribution of the iodinated proteins were obtained from autopsies performed four hours after administration of the protein. Table 4 summarizes these data. All organs except thyroid and stomach contained less than 0.4 per cent radioactivity per 10 Gm. of tissue. The highest level of radioactivity was in the thyroid glands. The stomach had the next highest concentration of radioactivity, with no definite pattern of protein selectivity. The major excretory routes were urinary and biliary. Approximately 7 to 15 per cent of the total plasmin radioactivity was excreted via the kidney. VariDase and purified urokinase exhibited similar urinary patterns. The urinary counts represent total excretion during the four-hour experimental period. Bile excretion percentages ranged from 0.2 to 4.5 per cent.

### Discussion

With the aid of an $^{131}$I label, the distribution and metabolism of components of the fibrinolysin system have been studied. Prior to use, it was necessary to establish the effect of iodination exerted on the in vitro activity of the various proteins. It is difficult to compare the results among the various plasmin preparations because each represents a different activation technique just prior to or directly after iodination. However, it would appear from the in vitro activity data that the number of atoms per mg. of protein is critical. The proteins that showed the lowest degree of inactivation were those with the smallest number of iodine atoms. It is well established that physical-chemical properties of proteins vary with the degree of iodination.$^{13}$ The progressive decrease in proteolytic activity exhibited by pepsin with increasing number of iodine atoms per molecule is well known.$^{17}$ Decrease in fibrinolytic activity following iodination may be due to (1) occupation by
Table 2

Table 2: In Vivo Clot Localization of 1'3'-Tagged Components of the Fibrinolysin System

<table>
<thead>
<tr>
<th>Component* (1'31 indicates position of radioactive tag)</th>
<th>No. of dogs</th>
<th>Dose</th>
<th>Per cent injected radioactivity per 100 Gm. clot 1 hour after injection</th>
<th>Clot lysis after 24 hours†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasminogen + SK → plasmin 1'31</td>
<td>4</td>
<td>30 U./Kg.</td>
<td>1.05</td>
<td>++</td>
</tr>
<tr>
<td>Human plasminogen1'31 + SK → plasmin</td>
<td>2</td>
<td>30 U./Kg.</td>
<td>1.00</td>
<td>++</td>
</tr>
<tr>
<td>Varidase1'31 (SK + SD)</td>
<td>2</td>
<td>1.5 × 10^6 U./Kg.</td>
<td>0.01</td>
<td>−</td>
</tr>
<tr>
<td>Purified SKT 1'31</td>
<td>2</td>
<td>2 × 10^6 U./Kg.</td>
<td>0.15</td>
<td>−</td>
</tr>
<tr>
<td>Human plasminogen + UK → plasmin 1'31</td>
<td>2</td>
<td>30 U./Kg.</td>
<td>1.00</td>
<td>++</td>
</tr>
<tr>
<td>Human plasminogen 1'31 + UK → plasmin</td>
<td>2</td>
<td>30 U./Kg.</td>
<td>0.95</td>
<td>++</td>
</tr>
<tr>
<td>Purified UK 1'31</td>
<td>2</td>
<td>1 × 10^6 U./Kg.</td>
<td>0.20</td>
<td>−</td>
</tr>
<tr>
<td>Human plasminogen 1'31</td>
<td>3</td>
<td>30 U./Kg.</td>
<td>0.70</td>
<td>−</td>
</tr>
<tr>
<td>Human spontaneous plasmin 1'31</td>
<td>4</td>
<td>30 U./Kg.</td>
<td>0.54</td>
<td>+</td>
</tr>
<tr>
<td>Chloroform-activated bovine plasmin 1'31</td>
<td>2</td>
<td>10 U./Kg.</td>
<td>0.30</td>
<td>++</td>
</tr>
<tr>
<td>Albumin 1'31</td>
<td>2</td>
<td>150 mg./Kg.</td>
<td>0.10</td>
<td>−</td>
</tr>
<tr>
<td>1'31</td>
<td>2</td>
<td>10 μg./Kg.</td>
<td>0.00</td>
<td>−</td>
</tr>
</tbody>
</table>

*SK = streptokinase; SD = streptodornase; UK = urokinase.

†Plasmin activity in RPMI units; Streptokinase activity in Christensen units; Urokinase activity in Ploug units.

††All clots were of standard size and weight; ++ = marked in vitro clot lysis; + = moderate in vitro clot lysis; − = no in vitro clot lysis.

iodine atoms of sites on the molecule essential for enzymatic activity; (2) depression of activity by iodine occupying closely related sites; (3) denaturation of the protein by the oxidative iodination procedure; or (4) a combination of any of the above possibilities. In view of the low degree of iodination, it seems likely that the partial inactivation observed was due to damage caused by some step in the procedure rather than to the effect of the iodine introduced per se. The mechanism of this inactivation is currently under investigation.

Of interest is the retention of activity by urokinase and streptokinase following iodination. The degree of iodine labeling of streptokinase is almost identical to that obtained by Fletcher et al. 18 0.2 atoms per molecule of streptokinase (assuming the same molecular weight of 60,000). These investigators also encountered no loss of biochemical activity with as much as 1 atom of iodine per molecule. The ability of plasminogen to be activated by streptokinase following iodination was only slightly affected.

The specific localization of plasmin onto preformed clots with subsequent clot lysis was a consistent observation. Clot localization and lysis occurred in plasmin-treated dogs, even in the absence of free, circulating fibrinolytic activity. Radioactivity data, however, revealed the presence of some circulating form of plasmin, presumably in complex form with an inhibitor. Thus, confirmation is obtained for the concept of a circulating plasmin inhibitor which reversibly complexes with plasmin. 19,20 Recent in vivo and in vitro investigations in our laboratory 21 have demonstrated that this plasmin-inhibitor complex dissociates in the presence of a fibrin substrate, the plasmin preferentially attaching itself to the fibrin. The antiplasmin would thus appear to act both as a physiological protector of plasmin, preventing its immediate degradation, and as a transport system, carrying and releasing the plasmin preferentially to fibrin substrates. This mechanism would also protect normal plasma proteins from digestion by the proteolytic ability of plasmin.

The degree of plasmin localization onto clots was 100 times greater than that exhibited by urokinase or streptokinase. In these activator-treated dogs, there occurred no significant clot lysis. Spontaneously activated...
plasmin did not localize to as great an extent as streptokinase- or urokinase-activated plasmin. Differences in the biochemical characteristics between spontaneously activated and kinase-activated plasmins have been reported before.\(^2\)\(^{,\,}20\) Notably, kinase-activated plasmins were found to be more specific for fibrin than spontaneously activated plasmin.\(^2\)\(^{,\,}20\) Spontaneously activated plasmin also caused less hypotension and had less effect on clotting factors than kinase-activated plasmins.\(^2\)\(^{,\,}22\) Clinically, spontaneous plasmin, on a unit basis, was less effective than urokinase- or streptokinase-activated plasmin. The difference in activator activities between spontaneous- and streptokinase- or urokinase-activated plasmin may account partly for the differences in response.

The localization of plasminogen onto clots was an interesting finding. It may reflect the possible physiological role played by plasminogen, incorporating into or adsorbing onto intravascular thrombi and aiding their dissolution after activation.

The plasma clearance data are difficult to interpret. At least two processes were seen, an initial rapid one and a subsequent slower one. The fast process may represent rapid removal of denatured proteins and smaller iodinated contaminants by filtration from the vascular bed and uptake partly by the reticuloendothelial system. The slower process re-
Table 4

Distribution of $^{125}$I-Labeled Components of the Fibrinolysin System (Four Hours After Injection)

<table>
<thead>
<tr>
<th>Component (I$^{125}$ indicates position of tag)</th>
<th>Dose*</th>
<th>Per cent of injected activity</th>
<th>Per cent of injected activity total excretion in 4 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human plasminogen + SK $\rightarrow$ plasmin $^{125}$</td>
<td>30 U./Kg.</td>
<td>4.39 0.95 7.76 0.58</td>
<td></td>
</tr>
<tr>
<td>Human plasminogen $^{125}$ + SK $\rightarrow$ plasmin</td>
<td>30 U./Kg.</td>
<td>0.78 0.80 9.33 3.13</td>
<td></td>
</tr>
<tr>
<td>Human plasminogen $^{125}$</td>
<td>30 U./Kg.</td>
<td>1.88 1.27 10.13 1.43</td>
<td></td>
</tr>
<tr>
<td>Varidase™ (SK + SD)</td>
<td>1.5 X 10$^6$ U./Kg.</td>
<td>13.80 0.80 11.64 0.88</td>
<td></td>
</tr>
<tr>
<td>Purified SK $^{125}$</td>
<td>2 X 10$^6$ U./Kg.</td>
<td>13.45 1.35 1.55 0.20</td>
<td></td>
</tr>
<tr>
<td>Human plasminogen + UK $\rightarrow$ plasmin $^{125}$</td>
<td>30 U./Kg.</td>
<td>0.98 1.10 6.79 0.11</td>
<td></td>
</tr>
<tr>
<td>Human plasminogen $^{125}$ + UK $\rightarrow$ plasmin</td>
<td>30 U./Kg.</td>
<td>1.05 0.50 7.50 0.30</td>
<td></td>
</tr>
<tr>
<td>Purified UK $^{125}$</td>
<td>1 X 10$^6$ U./Kg.</td>
<td>14.08 0.80 18.08 1.10</td>
<td></td>
</tr>
<tr>
<td>Human spontaneous plasmin $^{125}$</td>
<td>30 U./Kg.</td>
<td>4.78 0.55 12.75 2.46</td>
<td></td>
</tr>
<tr>
<td>Human spontaneous plasmin $^{125}$</td>
<td>30 U./Kg.</td>
<td>1.38 0.60 17.8 0.78</td>
<td></td>
</tr>
<tr>
<td>Chloroform-activated bovine plasmin $^{125}$</td>
<td>10 U./Kg.</td>
<td>1.70 0.25 6.67 0.65</td>
<td></td>
</tr>
<tr>
<td>Albumin $^{125}$</td>
<td>150 mg./Kg.</td>
<td>1.15 0.03 0.34 1.70</td>
<td></td>
</tr>
<tr>
<td>1$^{125}$</td>
<td>10 mcg./Kg.</td>
<td>11.4 0.13 9.85 1.71</td>
<td></td>
</tr>
</tbody>
</table>

*Plasmin activity in RPMI units (3); Streptokinase (SK) activity in Christensen units; Urokinase (UK) activity in Ploug units.

†Liver, spleen, pancreas, salivary glands, esophagus, duodenum, trachea, lung, heart, kidney, adrenals, and gonads contained less than 0.4 per cent of injected activity per 10 Gm. of tissue.

The distribution of the material between intravascular and extravascular compartments. Part of both processes undoubtedly is due to metabolic degradation and subsequent excretion by kidney and liver. Plasmin molecules are known to undergo a series of peptide splits and eventual inactivation in vitro. Localization onto clots represents only an insignificant route of removal for the injected labeled plasmin. Of all the tissues studied, the thyroid took up the largest percentage of injected radioactivity. This action may take place during decomposition of the labeled compounds. The stomach contained the next highest radioactivity level, which may represent exchange of chloride for iodide by the gastric mucosa.

The hypothetical case cannot be excluded that in some of the preparations, chiefly the contaminants were tagged and not the proteins aimed at. Indeed such a case has been presented for streptokinase by De Renzo and Siiteri. However, Fletcher et al. claimed successful iodination of streptokinase. In our experiments, streptokinase did not cause clot lysis in dogs, nor was there any significant adsorption of radioactivity onto the clot. On the other hand, plasminogen activated with iodine-labeled streptokinase did produce clot lysis and also showed a high degree of localization on fibrin clots.

The experiment showing persistence of radioactivity at a time when no free plasmin activity could be observed by fibrinolytic assay (fig. 6) deserves further comment. If the assumption on which all considerations in this paper have been based is correct, namely, that plasmin was the predominant labeled component injected, then these results must mean that practically all the injected plasmin is neutralized by an inhibitor within 30 minutes after its injection. The presence of antiplasmin in the circulation is a well-known fact. Its amount has been estimated by Norman to exceed 30-fold the potential proteolytic activity of all the intrinsic plasminogen. That the formation of this neutralizing complex does not render the injected plasmin ineffective is shown by previous experiments which demonstrated in dogs lysis of clots admitted into the circulation at a time when all previously injected plasmin had been neutralized. Similarly, plasmin-antiplasmin complexes which showed no caseinolytic activity in vitro...
were able to lyse fibrin clots in vivo in dogs. On the basis of these observations, it can be postulated that fibrin, when in contact with antiplasmin, competitively removes plasmin from its combination with antiplasmin. Support for the ability of fibrin to compete effectively for plasmin when in the complex form is furnished by previous in vitro experiments.20

This study was carried out with some of the best preparations of proteins of the fibrinolytic system available at the time. Yet it remains a weakness of the experiments that these proteins were not available in pure form.

Summary

The distribution, metabolism, and excretion of intravenously administered I131-labeled components of the fibrinolytic system were studied in dogs. Iodination of plasmin tended to decrease slightly its in vitro fibrinolytic activity. Inactivation appeared to depend on degree of iodination. Iodination of streptokinase or urokinase did not decrease their plasminogen activator potential. All plasmins and plasminogen, regardless of the position of the iodine tag, adsorbed to preformed clots in the dog. Spontaneously activated human and chloroform-activated bovine plasmin adsorbed to a lesser extent than streptokinase- or urokinase-activated human plasmin. Clots removed from plasmin-treated dogs lysed in vitro within 24 hours. However, streptokinase or urokinase alone, on the basis of radioactivity measurements, did not exhibit any affinity for clots, nor did they cause any clot lysis. Plasma clearance curves revealed the presence of at least two processes in all preparations: a fast one (average half-life four minutes) responsible for the removal of over 60 per cent of the injected radioactivity and a slower process with a biological half-life greater than four hours. Four hours after the injection of labeled compounds, the thyroid and stomach were the only organs which contained significant percentages of the injected radioactivity. Major excretory routes for the radioactivity were the urinary and biliary systems. Persistence of circulating radioactivity at a time when no free fibrinolytic activity could be determined in the blood was interpreted as complex formation between plasmin and antiplasmin.

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The authors express their indebtedness to Dr. Gabor Markus for his many helpful suggestions as well as his critical review of this manuscript. The assistance of the following summer fellowship students is also acknowledged: Mr. Paul Gandel, Tufts University; Mr. Stephen Kass, Brown University; and Mr. Nelson Schiller, Union College, Pennsylvania. Fraction III of human blood was kindly supplied by Dr. Perl, American National Red Cross Blood Program.

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