Stimulation of Fibrinogen Synthesis: A Possible Functional Role of Fibrinogen Degradation Products

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Fibrinogen production, measured by the rate of incorporation of $^{75}$Se-selenomethionine into newly synthesized circulating fibrinogen, was determined in rabbits administered urokinase and ancrod to generate degradation products of fibrinogen or fibrin in vivo. Fibrinogen degradation products appeared in elevated titers in metabolically normal animals after receiving infusions of urokinase. Fibrinogen production was increased fourfold to fivefold, while the basal synthesis of nonclottable proteins was unaffected. In rabbits rendered afibrinogenemic by intravenous ancrod, 2 U/kg, fibrinogen production was not accelerated unless 150 mg of homologous fibrinogen were infused slowly into the afibrinogenemic animals at the time of peak generation of degradation products. This technique produced a threefold increase in fibrinogen synthesis. When partial defibrinogenation was accomplished with ancrod, 0.75 U/kg over 1 hr, elevated titers of degradation products were detected and, subsequently, fibrinogen synthesis was enhanced twofold. These data suggest that ancrod at 2 U/kg may convert fibrinogen to fibrin so rapidly that only fibrin degradation products are formed. These probably do not influence fibrinogen synthesis: however, if fibrinogen is available as a substrate for the activated plasminogen-plasmin system, fibrinogen degradation products may be generated and subsequently may mediate the stimulation of fibrinogen synthesis.

Stimulation of fibrinogen synthesis was observed in rabbits following slow intravenous administration in milligram quantities of fibrinogen degradation products D and E (FDP-D, FDP-E) prepared in vitro. In contrast, basal fibrinogen production was unaffected by infusions of fibrin degradation products (fdp) obtained in vitro by plasmin lysis of crosslinked thrombin clots and non-crosslinked clots produced by thrombin or ancrod, a coagulant enzyme purified from the crude venom of the Malayan pit viper (Agkistrodon rhodostoma). Furthermore, rapid defibrinogenation with ancrod and subsequent in vivo generation of fibrin degradation products in high titers also failed to enhance fibrinogen production in the rabbit. These results suggested that FDP, specifically FDP-D and FDP-E, might mediate the stimulation of fibrinogen synthesis, directly or indirectly, while fdp do not.

The purpose of this study was to examine the effects on fibrinogen synthesis of the FDP presumably generated in vivo after infusions of urokinase or homologous fibrinogen administered to rabbits with ancrod-induced afibrinogenemia. In addition, fibrinogen production was evaluated in rabbits partially defibrinogenated with ancrod. The data suggest that stimulated fibrinogen synthesis may occur in association with the in vivo formation of FDP. Rapid and complete defibrinogenation by ancrod does not alter basal fibrinogen production, possibly because fdp are generated exclusively or because FDP are not generated in adequate titer or specificity.

MATERIALS AND METHODS

Male New Zealand white rabbits, weighing 2.0–3.0 kg, were caged individually in air-conditioned quarters with laboratory chow and water available ad libitum for at least 4 days before studies were instituted. Only healthy animals with normal baseline fibrinogen concentrations and hematocrit values were used.

Urokinase extracted from human urine (Winthrop Laboratories, New York, N.Y.) was administered intravenously to rabbits as a loading dose of 4400 CTA U/kg over 25 min, followed by continuous infusion of 4400 CTA U/kg/hr for 4 hr through a 23-gauge needle (Butterfly-23 infusion set; Abbott Laboratories, North Chicago, Ill.) inserted into the right marginal ear vein. Ancrod (Venacil; Abbott Laboratories, North Chicago, Ill.), supplied in concentrations of 100 U/ml, was mixed in 30 ml of sterile isotonic saline and infused in the same manner. Rabbits received either 2 U/kg body mass of ancrod over 1 hr to achieve complete defibrinogenation or 0.75 U/kg body mass for 1 hr to obtain partial defibrinogenation. Control animals were given equal volumes of saline or saline followed by 150 mg homologous fibrinogen (vide infra).

Homologous fibrinogen was purified from citrated plasma according to the technique of McFarlane. Cryofibrinogen was removed during the purification process. The resulting fibrinogen was 90%–98% clottable, and purity was analyzed by reduced and nonreduced sodium dodecyl sulfate (SDS) polyacrylamide electrophoresis and by immunodiffusion. For experimental use, lyophilized fibrinogen was dissolved in 30 ml sterile water to a concentration of 5 mg/ml and infused over 1 hr into animals previously rendered afibrinogenemic by ancrod, 2 U/kg. Infusions of exogenous fibrinogen have been demonstrated previously not to influence the rate of incorporation of $^{75}$Se-selenomethionine ($^{75}$SeM) into de novo synthesized fibrinogen. Each preparation used for infusion in this study was tested for endotoxin by means of the Limulus lysate assay of Levin and Bang.

Blood samples were obtained at baseline, following infusions, immediately before isotope injection, and hourly after $^{75}$SeM admin-
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Fibrinogen synthesis—degradation products

Citrate-O.20

Ear vein into siliconized glass tubes containing 0.13 M sodium citrate—0.20 M ε-amino caproic acid (ε-ACA) (1:9 v/v). Plasma was prepared by centrifuging whole blood at 5500 g for 10 min at 4°C and was used subsequently for determination of fibrinogen concentration and radioactivity and for the detection of fibrinogen-fibrin degradation products (FDP-fdp).

Titers of FDP-fdp were determined by the tanned red cell hemagglutination-inhibition immunoassay, modified for use in rabbits. Normal values in our laboratory are ≤ 1:8 and represent the highest serum dilution that prevented agglutination of fibrinogen-coated red cells by anti-rabbit fibrinogen antibodies. This technique detects less than 1.0 μg fibrinogen/ml plasma.

The effectiveness of ε-amino caproic acid (ε-ACA) as an in vitro inhibitor of fibrinogen-olysis by activated plasmin was studied in plasma specimens collected in 0.13 M sodium citrate—0.20 M ε-ACA (9:1 v/v) from animals administered ancred and urokinase. The presence of residual plasmin activity was excluded by examining the samples on heated fibrin plates (Enzo Diffusion fibrin plate test; Hyland Products, Costa Mesa, Calif.). Plasma samples were also subjected to repeated reduced and nonreduced SDS polyacrylamide gel electrophoretic analysis and to determinations of FDP-fdp over a 12-hr period following their collection to ensure that no further fibrin/fibrinogen proteolysis had occurred. Similar studies were performed simultaneously, substituting the potent serine protease inhibitors, diisopropylfluorophosphate and phenylmethanesulfonyl fluoride, for ε-ACA during plasma collection. The effectiveness of ε-ACA (0.02 M final concentration) impeding proteolytic activity of plasmin in vitro appeared equivalent to that of the other inhibitors.

35SeM (20 μCi) was injected into the right marginal ear vein 5 hr after completing the infusions of urokinase, ancrod, or ancrod followed by fibrinogen. De novo fibrinogen synthesis was measured by the rate of appearance of the isotope in circulating fibrinogen.

Fibrinogen was assayed for concentration and for radioactivity employing the technique of Lerner et al., as previously modified by this laboratory. Samples were analyzed at 282 nm (Hitachi-Perkin-Elmer spectrophotometer, Model 139, Hitachi, Tokyo, Japan) against a urea blank, using 1.617 as the extinction coefficient for rabbit fibrin dissolved in alkaline urea. Incorporation of 35SeM was calculated as the percent of the administered dose detected in circulating fibrinogen as follows:

\[
\frac{\text{cpm/mg Fibrinogen} \times \text{mg Total circulating fibrinogen} \times 100}{\text{Total cpm } 35\text{SeM injected}}
\]

Plasma volume was assumed to be 40 ml/kg body weight. This approach allowed comparison between different experimental groups with varying weights. Extensive studies were performed to evaluate the specificity of 35SeM incorporation into newly synthesized fibrinogen. 35SeM incorporated into plasma proteins was distinguished from free and nonspecifically bound 35SeM by treating portions of the plasma samples obtained following administration of 35SeM with 1.0 N sodium bisulfite to destroy nonspecific selenosulfide bonds. The proteins were precipitated with 20% trichloracetic acid (TCA) and washed repeatedly with cold 10% TCA; the radioactivity of the supernatant, washings, and protein precipitate was then determined. A similar procedure was performed on the specimens after removing the fibrin clot. The nonclottable proteins remaining in the clot liquor were measured, and the radioactivity of their TCA precipitates determined. The data were then inserted into the above formula, which was modified to calculate the percent 35SeM incorporated into nonclottable protein.

Contamination of fibrinogen by other circulating radiolabeled proteins generated during the experiments was assessed by incubating unlabeled rabbit plasma and solutions of unlabeled purified rabbit fibrinogen with equal volumes of serum from rabbits administered 35SeM 24 hr previously. The fibrinogen was clotted and dissolved in alkaline urea and its radioactivity measured. Similar studies were conducted in unlabeled plasma to which 35SeM had been added to give 10,000 cpm of 35SeM/ml of plasma. Furthermore, plasma samples from rabbits injected with 35SeM 6 hr previously were immunoprecipitated with optimal quantities of goat anti-rabbit fibrinogen antibody, as determined by an immunoprecipitation curve. After centrifugation and washing, the radioactivity of the supernatant and precipitate was determined.

Additional evidence for the specific incorporation of 35SeM into de novo synthesized fibrinogen was obtained by precipitating the fibrinogen with 25% saturated ammonium sulfate from the plasma of rabbits administered 35SeM 6 hr previously. This material was subjected to SDS polyacrylamide electrophoresis in reduced and nonreduced forms, and each gel band was cut and measured for radioactivity. Multiple specimens were collected from each rabbit before infusions of urokinase and at 0, 3, and 5 hr following 35SeM injection for determination of serum haptoglobin levels and incorporation of 35SeM into haptoglobin.

The metabolic alterations of fibrinogen after administration of ancrod and ancrod followed by fibrinogen were evaluated by subjecting plasma samples obtained immediately before and 1 hr following infusions to gel filtration over columns of Sepharose 4B (Pharmacia) according to the technique described by Bell et al. Fibrinopeptide A release with ancrod or thrombin was then determined from those protein peaks that reacted with anti-rabbit fibrinogen antibody on immunodiffusion or counterimmunoelectrophoresis.

Mean, standard deviation, standard error, and comparative group analysis were computed by conventional methods.

RESULTS

Hematocrit values in experimental and control rabbits remained normal and essentially unchanged during the sampling period for determination of plasma fibrinogen radioactivity. Endotoxin was not detected in the urokinase or ancrod preparations assayed prior to infusion, and less than 10 ng/ml of endotoxin contamination was measured in solutions of purified fibrinogen.

The procedures employed to evaluate the specificity of the radioactive label for de novo synthesized fibrinogen indicated that 35SeM functioned as an efficient amino acid cohort. Nonspecific selenosulfide binding of 35SeM was insignificant, with 93% ± 3.0 (SD) of the plasma radioactivity precipitable by TCA 6 hr after isotope administration. There was 96% ± 2.0 (SD) plasma radioactivity precipitable by goat anti-rabbit fibrinogen antibody. After incubation of unlabeled rabbit plasma or purified fibrinogen with 35SeM or radioactive serum, less than 3% of the original radioactivity was detected in clotted fibrinogen. Furthermore, the fibrinogen purified from plasma of rabbits that had received 35SeM previously was associated with significant amounts of radioactivity after SDS polyacrylamide gel electrophoresis.
Effect of Urokinase on Fibrinogen Synthesis

Urokinase (4400 CTA U/kg loading dose followed by continuous infusion of urokinase 4400 CTA U/kg/hr for 4 hr) was administered intravenously to a group of 6 rabbits. There was a short-lived and slight decline in the plasma fibrinogen levels following completion of the infusions (Fig. 1); however, within 5 hr, the plasma fibrinogen concentration approached baseline values. After an additional 5 hr, plasma fibrinogen had decreased significantly to less than 1.40 g/liter. This degree of hypofibrinogenemia disappeared by 24 hr, as indicated by return to baseline levels in the 24-hr sample. In the 18 control animals given saline, the plasma fibrinogen concentration remained stable and within the normal range.

Abnormally elevated titers of FDP-fdp were detected in the experimental group within the first hour after initiating urokinase infusions. These titers subsequently peaked in the range of 1:128–1:256 at the completion of infusion and gradually decreased thereafter to normal levels by 5 hr, just prior to injection of \(^{75}\)SeM. In the control group, the FDP-fdp remained normal throughout the study period.

Analyses of \(^{75}\)SeM incorporation into clottable protein (fibrinogen) was performed in each animal and is illustrated in Fig. 2. Fibrinogen synthesis was enhanced significantly 6 hr after terminating urokinase infusion (1 hr postinjection of isotope). Incorporation of \(^{75}\)SeM into fibrinogen continued to rise over 24 hr. In contrast, levels of \(^{75}\)SeM-labeled fibrinogen in control rabbits were maximal 4–5 hr after \(^{75}\)SeM injection (9–10 hr following saline infusions) and remained constant over the next 24 hr (Fig. 2).

The specificity of stimulation of fibrinogen synthesis following infusions of urokinase was evaluated by \(^{75}\)SeM incorporation into total nonclottable serum proteins and serum haptoglobin. Although levels of \(^{75}\)SeM-labeled fibrinogen in rabbits that received urokinase were about three times those of control animals, the incorporation of isotope into nonclottable serum proteins and haptoglobin was unaffected. The percent incorporation of \(^{75}\)SeM into nonclottable serum proteins and haptoglobin 5 hr after injection of \(^{75}\)SeM was 4.98 ± 0.32 (SE) and 0.36 ± 0.07 (SE), respectively, in the urokinase group and 5.10 ± 0.26 (SE) and 0.32 ± 0.04 (SE), in the controls. Abnormal bleeding was not observed in animals receiving urokinase.

Effect on Fibrinogen Synthesis of Partial Defibrinogenation by Ancrod

Partial defibrinogenation was attempted in a group of 13 metabolically normal rabbits by the intravenous administration of ancrod, 0.75 U/kg over 1 hr. The effect of ancrod was variable; however, hypofibrinogenemia (1.34 ± 0.13 g/liter) was produced successfully in 8 rabbits (Fig. 3). The remaining 5 rabbits were rendered afibrinogenemic, with unmeasurable plasma fibrinogen levels. Mean titers of FDP-fdp increased from normal (≤1:8) to titers of 1:512 (range 1:256–1:1024) in the hypofibrinogenemic group and to levels of 1:4096 (range 1:2048–1:8192) in the afibrinogenemic group. In the 18 control animals who received saline, FDP-fdp remained normal. Fibrinogen synthesis was measured in each group by following the incorporation of \(^{75}\)SeM injected. The percent incorpo-
Fig. 3. Effect on fibrinogen concentration of partial defibrinogenation by ancrod. Of 13 rabbits administered ancrod 0.75 U/kg over 1 hr, 8 successfully achieved partial defibrinogenation and are represented here. There was a dramatic rebound in the fibrinogen levels of this group 24 hr following partial defibrinogenation. The control animals received saline. Values for the 5 rabbits rendered afibrinogenemic are not shown. Means ± SE for 8 animals are shown.

Effect on Fibrinogen Synthesis of Infusions of Ancrod and Fibrinogen

A group of 17 rabbits was rendered afibrinogenemic by the infusion of ancrod, 2 U/kg over 1 hr. Following a 1-hr rest period, 7 animals received a slow infusion of 150 mg purified homologous fibrinogen over the next hour. This represented approximately 50% of the rabbit’s plasma fibrinogen pool,22 or 30% of total body pools of fibrinogen.23,24 After a lag period of 5 hr following fibrinogen administration, 75SeM was injected for evaluation of fibrinogen synthesis. The controls consisted of the remaining 10 animals, which were completely defibrinogenated and subsequently received saline instead of fibrinogen.

In all rabbits given ancrod, plasma fibrinogen concentrations declined precipitously from preinfusion values of 2.58 ± 0.19 g/liter to undetectable levels immediately after infusion. Fibrinogen levels 24 hr later had risen to 3.15 ± 0.31 g/liter in the ancrod-fibrinogen group and 1.23 ± 0.28 g/liter in the controls. Residual coagulant activity of ancrod was examined in plasma specimens obtained just prior to fibrinogen infusions by incubating 0.1-ml aliquots with 0.3 ml of fresh normal rabbit plasma at 37°C. No clot formation was observed over 5 hr. Plasma samples were clottable following fibrinogen administration. Mean titers of FDP-fdp were elevated to 1:16,000 (range 1:2000–1:64,000) after ancrod, and immediately following fibrinogen infusions, had increased further to 1:64,000 (range 1:8000–1:132,000).

Plasma 75SeM-labeled fibrinogen, which was increased significantly in the ancrod-fibrinogen group 1 hr after injection of isotope (6 hr following fibrinogen infusion), continued to rise over the 24-hr period. This is compared to the normal basal rates of fibrinogen production maintained in the controls throughout the study (Fig. 5).

Numerous unsuccessful attempts were made to establish that the degradation products in ancrod-treated afibrinogenemic animals were predominantly fdp versus FDP. The latter presumably would be...
In contrast, the intravenous administration of ancrod to man and animals induces an immediate and rapid depletion of plasma fibrinogen, which may persist for days even though basal fibrinogen synthesis is not significantly affected. An explanation for these conflicting results has not been available. Reports attributing the stimulation of fibrinogen synthesis to feedback effects of hypofibrinogenemia per se have not been substantiated. Experimental data from animals suggest that the FDP-fdp generated in vitro during defibrinogenation may provide a stimulus for fibrinogen production. These findings were supported by studies that described enhanced fibrinogen synthesis following infusions of FDP produced in vitro. However, basal fibrinogen production remained unaltered by infusions of fdp prepared in vitro by lysis of crosslinked and non-crosslinked fibrin formed by thrombin (in the presence or absence of calcium chloride) and ancrod. These studies imply that a physiologic difference exists between the ability of FDP and fdp to stimulate fibrinogen synthesis.

The present study was undertaken to provide insight into these observations and suggested that the augmentation of basal fibrinogen synthesis may be mediated by FDP, generated in vivo, but not by fdp, in this case, non-crosslinked and formed during ancrod infusion.

A 5-hr interval between infusions of experimental agents and $^{75}$SeM was utilized in accordance with the results of Barnhart and coworkers, who observed peak uptake of infused FDP into canine liver reticuloendothelial cells after 4 hr, with maximum evidence of hepatocyte fibrinogen synthesis after 5 hr. Our experimental model also allowed for the in vivo rates of disappearance of FDP from the plasma circulation of rabbits. In addition, previous studies indicate...
that the rate of incorporation into fibrinogen of radio-
labeled amino acids directly depends on the interval
elapsing between infusion of stimulating agents and
isotope. Preliminary work in our laboratory confirmed
this. Basal fibrinogen synthesis may have to be stimu-
lated before de novo synthesized 35S-methylene-
fibrinogen enters the plasma from the hepatocyte in quantities
and rates greater than those observed in controls.24
Specific stimulation of fibrinogen synthesis may
subsequently divert labeled amino acid away from
incorporation into other liver cell proteins.24

Intravascular defibrinogenation by ancord and
thrombin involves different processes. Thrombin
cleaves both fibrinopeptides A and B in the conversion
of fibrinogen to fibrin monomer41-43 and then promotes
crosslinking in the presence of calcium by activating
factor XIII.44,45 In addition, thrombin can initiate the
crosslinking and release reaction of platelets46 and
activate the fibrinogenolytic system in vitro, and
presumably in vivo, as well.47 Ancrod, on the other
hand, converts fibrinogen to fibrin through the cleav-
age of fibrinopeptide A (FPA) alone47-50 and may
remove a small part of the α chain of the molecule.50
The purified venom extract does not activate factor
XIII,51,52 trigger the platelet release reaction,53 or
directly activate plasminogen to plasmin in vitro.54
Nevertheless, fibrinolysis does occur in vivo following
ancrod administration.49,50,51,54-56 Unlike thrombin,
ancrod infusions do not affect platelet counts,50
platelet turnover,51 or synthesis or catabolism of
fibrinogen3-9 or prothrombin.19 Levels of other coagu-
lation factors also remain unaltered.54,57 Therefore, it
is not unexpected that FDP might differ from fdp
derived from crosslinked or non-crosslinked fibrin,
both in a structural sense and a physiologic sense.

The data in the present study suggest that the fdp
generated in high titers following complete defibrino-
genation by ancord were not capable of mediating the
stimulating fibrinogen synthesis; however, if fibrino-
gen was available as a substrate for the activated
plasminogen-plasmin system, fibrinogen synthesis was
enhanced significantly, possibly mediated by the
resulting FDP. This was achieved in rabbits by either
partial defibrinogenation with ancord or by the infu-
sion of homologous fibrinogen into animals previously
rendered afibrinogenemic by ancord.

Attempts to confirm the increased predominance of
FDP following fibrinogen administration to animals
rendered afibrinogenemic by ancord were unsuccessful
using gel filtration of plasma and analysis of FPA
release from protein peaks immunologically recog-
nized by antifibrinogen antibody. However, fibrinogen
was infused at a time when plasmin activity was high
and the residual in vitro and in vivo58 coagulant
activity of ancord was negligible. A rise in titer of
FDP-fdp was detected and strongly supports the idea
that FDP were generated.

The importance of FDP as possible mediators of
fibrinogen production was demonstrated further by
their generation in vivo with urokinase. Urokinase, a
direct activator of plasminogen,59,60 is nonantigenic
and nonpyrogenic.61,62 This agent modestly reduces
plasma concentrations of fibrinogen and plasminogen
with associated elevations of degradation products,62
conceivably FDP alone in situations involving fibrino-
genolysis rather than thrombolysis. In the present
experimental model, fibrinogen synthesis was en-
hanced significantly following fibrinogenolysis by
urokinase. Previous investigations during thrombolytic
therapy62-65 in humans with urokinase or streptokinase
also revealed rapid restoration of plasma fibrinogen
levels.

The progressive decline in fibrinogen concentration
initially noted 6 hr after terminating urokinase (Fig.
1) is difficult to explain. No persistent fibrinogenolysis
was evident, and the fibrinogen assay technique was
not affected when experimental plasmas were mixed in
varying ratios (1:1, 1:9, 9:1) with fresh normal rabbit
plasma. The addition of homologous FDP fragment X'
in high titers (1:128-1:256) also failed to alter the
assay significantly (unpublished data). The gradual
decrease in fibrinogen levels may represent a real
phenomenon. It has not been reported previously;
however, it has not been looked for specifically. Most
studies have determined fibrinogen levels within hours
of terminating thrombolytic therapy and/or 24 hr
later. Data for intervening points are lacking.
Although the mechanism for our observations is
obscure, the phenomenon deserves to be confirmed
and investigated further.

Defibrinogenation by ancord may occur so rapidly
that fibrinogen is removed before it can react with the
plasmin that is generated. Consequently, only fdp may
be produced and basal fibrinogen synthesis remains
unaltered. The mechanism by which plasminogen is
activated in vivo by ancord infusion is unknown. Some
investigators propose that microthrombi produced by
ancrod stimulate a local release of plasminogen activa-
tor from the vessel endothelium,66 a concept that has
not been confirmed. Work is currently underway
in our laboratory to investigate the mechanism of plas-
minogen activation by ancord.

Examination of fibrinogen synthesis in vivo is
complicated by its acute phase reactant properties. In
addition, the relationship between synthesis, catabo-
lism, and total body distribution of the protein is
unclear. The current studies correlated increased $^{75}$SeM incorporation into clottable protein with net increases in plasma fibrinogen concentrations. Maneuvers intended to generate FDP in vivo were associated with enhanced fibrinogen production. No simultaneous qualitative or quantitative evidence for augmented production of total serum proteins or haptoglobin were found. Fibrinogen synthesis in animals may not be affected significantly by its plasma concentration and by its catabolic rate, which apparently proceeds at a rate proportional to its plasma level in the absence of ancrod-induced afibrinogenemia. Whether these relationships hold up in pathologic conditions remains speculative.

The observations from these and previous studies suggest that FDP and fdp may differ in their ability to influence fibrinogen production in rabbits. FDP generated in vitro and in vivo are associated with accelerated fibrinogen synthesis. The mechanism through which this is accomplished remains obscure, and the possibility remains that the enhanced fibrinogen production was not mediated exclusively by FDP. In contrast, fdp apparently do not share this stimulatory property whether they are infused after formation in vitro or presumably produced in vivo in high titers following rapid ancrod administration.

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