The Intestine as a Source of Plasminogen Activator Activity[1] (35327)

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Blood, lymph, and cerebrospinal fluid contain a beta globulin termed plasminogen which is a precursor of the proteolytic enzyme plasmin. This enzyme's affinity for fibrin is thought to be pronounced hence it has been implicated in the elimination of intra and extravascular fibrin deposits. By its ability to destroy fibrin it could provide a potential weapon for the prevention or treatment of thrombosis. Unfortunately, it is not yet known how this process can be utilized to the best advantage.

The activators of plasminogen are considered the second most significant components of the enzyme system. There are many. Several pharmacological agents act as exogenous activators as do the bacterial products streptokinase (1) staphylokinase (2) and endotoxin (3). Endogenous activator is present in urine (4), as urokinase, and in tissues, as tissue activator (5).

Despite a great deal of investigation on several aspects of plasminogen activation, particularly on its mode of activation (6), its inhibition by both natural and synthetic inhibitors (7), and its elimination by the liver (8), the information on the origin of the endogenous plasminogen activators responsible for the spontaneous lysis of blood clots is limited. Spontaneous lysis takes place at rates that vary greatly suggesting that the concentation of circulating activator is subject to marked fluctuations.

Evidence for a possible vascular origin was previously postulated by Mole (9) and subsequently provided by Kwaan *et al.* (10). Information gained from the present experiments suggests that considerable quantities of this material also come from the intestine. In view of its profound systemic effect we have to assume that in contrast to previously described endogenous activators, which are eliminated by the liver (8), this material traverses the liver under certain circumstances.

Methods and Materials. Three groups of mongrel dogs weighing between 15 and 20 kg were studied. The first two groups, one of 10 animals (group B) and one of 5 animals (group C) were pretreated on the day before the experiment with oral neomycin sulfate, three doses of 500 mg; a third group of 10 animals (group A) was not premedicated. On the morning of the experiment each animal was weighed and anesthetized with sodium Nembutal, administered intravenously (12 mg/lb). Catheters were placed in the femoral vessels under strict aseptic precautions. Immediately thereafter a blood sample was obtained from the arterial catheter in test tubes containing 0.06 ml of 15% EDTA solution in 0.2 mg/ml of potassium sorbate. After collection, each blood sample was immediately centrifuged at 2500 rpm for 5 min. The plasma was collected and duplicate euglobulin clot lysis time determinations were done by an established technique (11).

The animals of groups A and B were then subjected to total, one-stage hepatectomy by a previously described technique (12). The animals of group C underwent enterectomy followed by total, one-stage hepatectomy. The intestine, resected in block during the enterectomy, included rectum, colon, and small intestine up to but not including duodenum and pancreas. The blood supply of stomach, spleen, duodenum, and pancrease was intact following operation.

Blood samples were obtained 3 hr after resection of the liver. Again duplicate euglobulin clot lysis time determinations were performed.

Results. After induction of anesthesia nonpretreated animals exhibited low euglobulin

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clot lysis times, indicative of a marked plasminogen activator activity. Neomycin pretreatment prevented the appearance of this activity, the euglobulin clot lysis times in these animals (groups B and C) remained long. The difference between these 2 values is not significant. The difference in euglobulin clot lysis times between pretreated and untreated animals, however, is highly significant ($p<.001$).

After hepatectomy, euglobulin clot lysis times become shortened in nonpretreated animals. The difference between preoperative and postoperative values in group A is significant ($p<.05$). In the neomycin pretreated group the postoperative value is significantly lower than the preoperative value for this group ($p<.01$). In enterectomized, hepatectomized dogs, however, euglobulin clot lysis time values after surgery were slightly higher than before surgery. This difference was not significant (see Table I).

Discussion. Neomycin pretreatment interferes with the plasminogen activation observed after anesthesia. It does not affect or abolish the enzyme activation associated with hepatectomy. However, enterectomy prevents the appearance of both activities.

Neomycin, taken orally, lacks systemic effects and exerts its antimicrobial effect in the intestine only (13). The destruction of part of the animal's intestinal flora following neomycin pretreatment is associated with marked reduction of the "spontaneous" postanesthesia plasma fibrinolytic activity suggesting that the intestine is an important source of plasminogen activator activity. The presence of large quantities of plasminogen activator in untreated animals also suggests that under certain circumstances the liver, in contrast to its effect on other activators (8), may fail to eliminate this particular activator from the portal vein blood. Besides anesthesia, liver failure constitutes such a circumstance for fibrinolysis has been noted in moderate and severe hepatic failure particularly in patients with hepatic cirrhosis (14) following hepatic exclusion with porta-systemic shunting of blood (15) and during and after hepatic resection (16).

Liver failure, induced in the present experiment by one-stage, total hepatectomy, resulted in further enzyme activation in untreated and neomycin pretreated animals. Enterectomy preceeding hepatectomy on the other hand abolished this response.

The changes observed after surgery, in contrast to those found before surgery, lend themselves to a reasonable explanation. Substances deriving from the intestine may induce changes in the lytic mechanism that presumably are normally prevented from exerting their deleterious effects as a result of the liver's capacity to clear a host of undesirable factors from the portal vein blood. This concept is consistent with available information concerning the clearance activity of the liver for plasminogen activator (8) and various coagulative substances, *e.g.*, endotoxin (17), thromboplastin (18), and thrombin (19). In the absence of the liver the half-life of thrombin is greatly prolonged and thus it is able to exercise its deleterious systemic effects. Similarly, in those conditions that are associated with porto-systemic shunting of blood varying amounts of portal vein blood bypass the liver and thus escape its clearing activity. This, rather than actual failure to clear blood that derives from the intestine, may possibly explain the changes observed in the blood of patients with hepatic cirrhosis.

After induction of anesthesia the plasmino-

TABLE I.

		Euglobulin clot lysis time[a] (min)			
Group	No. of animals	After induction of anesthesia		After surgery	
A	10	38 ± 18	$p<.001$	21 ± 18	$p<.0001$
B	10	158 ± 67		94 ± 39	$p<.01$
C	5	187 ± 101		197 ± 72	

[a] Mean ± standard deviation.

gen activator activity of neomycin-pretreated dogs is significantly depressed. This suggests that the postanesthetic fibrinolytic response originates in the intestine and is possibly of microbial origin.

After hepatectomy, neomycin pretreatment fails to prevent the fibrinolytic response. Preceeding enterectomy, however, completely abolishes it. This suggests that the response also originates in the intestine. Whether it has a microbial origin is presently not certain.

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