Kinin Precursor in Experimental Pancreatitis* (33607)

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(Introduced by S. Warren)

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Interest continues regarding the role of -inin peptides as humoral mediators in acute pancreatitis. Plasma is an ample substrate for kinin, which can be activated from its precursor state—bound to alpha 2 globulin—by either trypsin or kallikrein. These enzymes, in turn, are normally present in the pancreas and are activated during the cell necrosis of acute pancreatitis. Well-known pharmacologic actions of kinins include pain production, vasodilatation, increased vascular permeability, hypotension, smooth muscle stimulation, and leukocyte aggregation. All of these are characteristically found during the course of acute pancreatitis.

Direct measurement of plasma kinin was extremely difficult and for this reason studies were carried out on the component parts of the kinin system. We previously reported the finding of increased kinin inhibitors during the course of experimental pancreatitis (1). Significant changes in the level of kinin precursors would add weight to the evidence indicating the kinin system in the pathologic physiology of acute pancreatitis.

Method. Ten splenectomized mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg of body wt.) and both femoral veins were cannulated, one for the removal of blood and the other for injection of serum albumin ^{131}I. Splenectomy was carried out 2 weeks previously to decrease the influence of splenic sequestration on the circulating blood volume. Pancreatitis was induced by intraductal infusion at 40 cm water pressure of a 20 ml mixture of 4% sodium taurocholate and 400,000 units of trypsin, adjusted to pH 8. Trypsin was previously assayed on a benzyl arginine ethyl ester substrate. Plasma volume was determined before operation and at 2, 4, and 6 hr after induction of pancreatitis using a Volemetron apparatus (Ames Company, Elkhart, Indiana). Hematocrit was determined by the micromethod. Plasma kininogen was determined by the method of Diniz and Carvalho (2) in which denatured plasma is exposed to an excess of trypsin, dried under pressure, and the residue resuspended in saline. Assays were carried out on an isolated, prepared, rat uterus. Isometric contraction was measured on a strain gauge and recorded on a direct writing oscillograph (Grass model no. 5DWCI).

In three of the dogs, peritoneal fluid was collected at 2, 4, and 6 hr after the onset of pancreatitis. Volume was recorded, hematocrit was determined, and the kininogen content was measured by the same methods.

Results. A devrease in the total circulating kininogen pool was demonstrated in all dogs during the first 6 hr of experimental pancreatitis. Circulating kininogen pool was calculated by multiplying the plasma volume by the kininogen concentration in micrograms per milliliter of plasma. Decrease varied from 11–48% with an average of 31.1% (Fig. 1). At the same time, plasma volume decreased an average of 28% (17–41%) and blood volume 19% (10–31%), while the hematocrit rose from an average control level of 40.4–48.8%. Circulating kininogen concentration averaged 1.49 μg/ml in the control specimens and 1.44 μg/ml in the 6-hour specimens —an average decrease of 3.4%.

In three dogs (nos. 8, 9, and 10) peritoneal fluid collections were made (Table I). The concentration of kininogen in the peritoneal fluid was remarkably constant, averaging 1.08 μg/ml. The total amount of kininogen recovered was therefore dependent on the volume of peritoneal fluid. Peritoneal fluid kininogen represented a substantial fraction

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TABLE I. Peritoneal Fluid Findings during First 6 hr of Pancreatitis.

Expt. no.	Total vol	Hematocrit	Total kininogen (μg)	Kininogen conc (μg/ml)	Plasma loss[a] (%)
8	204	3	235	1.15	220
9	288	1	295	1.02	61
10	121	3	130	1.07	41

[a] Percentage of circulating kininogen loss recovered in peritoneal fluid.

of that lost from the plasma, and in one experiment it was more than twice the plasma loss.

Discussion. The well-known fluid shift of acute pancreatitis has again been demonstrated (3). This is characterized by a decrease in blood volume, with greater loss of plasma than cellular elements, and a consequent rise

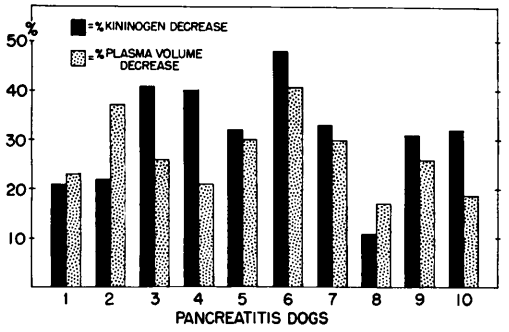

FIG. 1. Changes in plasma volume and total circulating kininogen.

in the level of hematocrit. Total circulating kininogen was consistently decreased, although the concentration in the plasma was not significantly altered. A substantial fraction of the kininogen was recovered in the peritoneal fluid—in one experiment it greatly exceeded the plasma loss. Ryan *et al.* (4) in the only other available study, also found a decrease in circulating kininogen and believed it to be the result of activiation to the vasoactive peptide. Simple shift of kininogen from plasma to peritoneal fluid may account for a good deal of the kininogen lost from the plasma however, and substantial amounts may also be lost into the retroperitoneal space and into the interstitial fluid of the pancreas—so prominent during acute pancreatitis. On the other hand, kininogen may be returned to the circulating plasma by way of lymphatic drainage of the peritoneal cavity, thus elevating the plasma level.

It is obvious that much more needs to be known about the balance between kininogen production and its activation before the present findings and those previously reported will allow valid conclusions to be drawn.

1. Nugent, F. W., Atendido, W. A., Bulan, M. B., and MacDonald, A. J., Nature 211, 207 (1966).

2. Diniz, C. R. and Carvalho, I. F., Ann. N. Y. Acad. Sci. 104, 77 (1963).

3. Elliott, D. E., Zollinger, R. M., Moore, R., and Ellison, E. H., Gastroenterology 28, 563 (1955).

4. Ryan, J. W., Moffat, J. G., and Thompson, A. G., Arch. Surg. 91, 14 (1965).

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