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The Lack of Gastric Tissue Fibrinolysis in Hemorrhagic Gastritis in the Rat (40442)

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Most body tissues contain fibrinolytic activator activity (FAA) (1–3). The role, if any, of gastric tissue fibrinolysis in gastric mucosal hemorrhage has not been established, but the finding of high FAA in the gastric juice of patients with hemorrhagic gastritis (3–5) suggested that local gastric fibrinolysis might be increased in the presence of hemorrhagic gastritis.

We report here the results of experiments designed to measure gastric mucosal FAA in rats with aspirin-induced and cold/restraint-induced hemorrhagic gastritis.

Methods. Male Sprague-Dawley rats weighing 95–345 g were housed in wire mesh cages and deprived of food but given free access to water for 24 hr prior to the experiment. Six rats were given acetylsalicylic acid, USP, (ASA), 250 mg/kg, suspended in 1 ml of methylcellulose by esophageal intubation with a soft plastic cannula (6–8). Six paired control rats were given 1 ml of 1% methylcellulose solution by similar esophageal intubation. Four hours later the stomachs were removed under ether anesthesia and the animals were sacrificed. The stomachs were opened, irrigated with cold saline (0.9% w/v) and handled as described below.

Four other rats were secured in standard restraint cages under light ether anesthesia (9, 10). Limbs and tail were taped to the cage and head movement was restricted by a suture securing the neck. Upon recovery they were placed in a refrigerator at 6° for 3 hr. These stressed rats and four paired nonrestrained, nonrefrigerated control rats were then sacrificed and their stomachs removed. All stomachs were examined under the dissecting microscope for the presence of hemorrhagic mucosal lesions. Lesions were defined as erosions of the gastric mucosa at least 1 mm in largest dimension.

Standard fibrin plates for assay of FAA were prepared according to a modified technique of Astrup and Mullertz (11, 2). Three assay plates were used: unheated standard fibrin plates, standard fibrin plates heated at 85° for 30 min (plasminogen inactivated) and antiplasmin plates containing episilon aminocaproic acid (EACA) in final concentration of 0.1%. Fibrin plate activity was controlled by innoculation of streptokinase, 25 units, onto randomly chosen plates from each batch prepared.

Two to four tissue specimens were obtained by punch biopsy of the antrum and the corpus of each stomach. Tissue specimens from the antrums of the experimental rats usually contained erosions. The submucosa was carefully dissected away from the mucosa which was blotted dry, weighed and placed luminal surface down on the fibrin plate. Multiple specimens from each stomach were innoculated on all three fibrin plates. The plates were incubated at 37° for 18 hr. FAA was measured by the area of lysis (mm^2) surrounding the mucosal specimen. Three area determinations were made for each specimen and the areas averaged. Statistical analysis of the data was done by Student's t test for paired samples.

Results. All aspirin treated and stressed rats had mucosal inflammation and hemorrhagic erosions of at least 1 mm in greatest dimension. All lesions were confined to the glandular portion of the stomach (antrum). Control rat stomachs were completely free of lesions. There was no significant difference in tissue FAA between control rats and those with either aspirin or stress induced gastritis (Tables I and II). The greater lytic activity in the standard unheated plates than in the heated and the EACA plates is due to tissue plasminogen activator rather than to free plasmin which is heat inactivated or to nonspecific proteolysis which is inactivated by EACA. The FAA of the antrum seems to be greater than that of the body of stomach ($p < 0.001$) but the difference between them disappears in the EACA plates indicating that it is due to gastric mucosal proteolytic enzymes.

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TABLE I. EFFECT OF ASPIRIN INDUCED HEMORRHAGIC GASTRITIS ON GASTRIC MUCOSAL FIBRINOLYTIC ACTIVATOR ACTIVITY (FAA) IN SPRAGUE-DAWLEY RATS.[a]

Treatment	Body			Antrum		
	Unheated plates	Heated plates	EACA plates	Unheated plates	Heated plates	EACA plates
	mm^2/mg					
ASA[b] (6)	22.6 ± 4.1	9.2 ± 1.6	7.0 ± 0.9	49.0 ± 4.9	14.8 ± 3.5	5.7 ± 1.0
None (6)	15.1 ± 1.8	7.0 ± 1.8	5.3 ± 0.7	37.9 ± 3.1	21.6 ± 5.5	4.8 ± 0.5
P Value[c]	.12	.48	.19	.08	.31	.40

[a] All values of FAA are expressed as mean (±SEM) area of lytic activity per mg of mucosa.
[b] Acetylsalicylic acid.
[c] *P* values were calculated by Student's *t* test.

TABLE II. EFFECT OF COLD/RESTRAINT STRESS-INDUCED HEMORRHAGIC GASTRITIS ON GASTRIC MUCOSAL FIBRINOLYTIC ACTIVATOR (FAA) ACTIVITY IN SPRAGUE-DAWLEY RATS.[a]

Group	Body			Antrum		
	Unheated plates	Heated plates	EACA plates	Unheated plates	Heated plates	EACA plates
	mm^2/mg					
Stress (4)	17.0 ± 1.9	3.9 ± 0.8	4.4 ± 0.6	57.7 ± 4.4	8.9 ± 3.4	4.7 ± 1.5
Control (4)	15.5 ± 2.5	4.5 ± 0.4	5.1 ± 0.9	63.7 ± 6.8	18.7 ± 7.5	5.3 ± 0.7
P Value[b]	.67	.52	.51	.49	.28	.79

[a] All values of FAA are expressed as mean area of lytic activity on fibrin plates ± SEM.
[b] *P* values were calculated by Student's *t* test.

Discussion. This study shows that gastric mucosal fibrinolytic activity is not increased in aspirin-induced or stress-induced hemorrhagic gastritis in rats and suggests that local gastric fibrinolysis is not likely to be an important factor in erosive hemorrhagic gastritic. Cox *et al.* (12–14) noted the possible role of fibrinolysis in peptic ulcer disease by finding free plasmin in the gastric veins, plasminogen activator in the gastric and duodenal mucosa and nonspecific proteolysis in the gastric juice of patients undergoing surgery for peptic ulcer. Nilsson *et al.* (4) reported four patients with hemorrhagic gastroduodenitis who had high gastric juice fibrinolytic activity without direct evidence of systemic fibrinolysis. Gastric juice from normal controls and from patients with hemorrhage from peptic ulcer did not have increased fibrinolytic activity. Successful antiplasmin therapy of bleeding gastric mucosal lesions has been described in a small number of patients, but the studies were not controlled (4, 15). Our results do not support the use of antiplasmin therapy in acute hemorrhagic gastritis.

Salicylates disrupt the gastric mucosal barrier by several independent mechanisms (16, 17), and also increase the fibrinolytic activity of white blood cells (18); however, ASA does not appear to produce accelerated gastric fibrinolysis. Recent evidence has emphasized instead the importance of acid and pepsin in inhibiting platelet aggregation and clot formation, thus prolonging gastroduodenal mucosal hemorrhage (19).

We conclude that local gastric tissue fibrinolysis cannot be considered to play a major role in initiating and maintaining acute aspirin or stress-induced hemorrhagic gastritis.

Summary. Gastric mucosal fibrinolytic activator activity was measured in rats with aspirin or cold/restraint stress-induced hemorrhagic gastritis, compared to paired controls. No significant difference in FAA was found in the gastric mucosa of the experimental and control rats. It is unlikely that local gastric fibrinolysis plays a major role in the causing or maintaining hemorrhagic gastritis.

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