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Changes in Gastric Mucosal Permeability Induced by Haemorrhagic Shock in the Anaesthetized Rat: Modulation by Acid

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Abstract

Gastric mucosal damage induced by haemorrhagic shock in the anaesthetized rat has been evaluated by studying changes in capillary-to-lumen clearance of fluorescein isothiocyanate (FITC)-labelled dextran.

Haemorrhagic shock (20 min ischaemia + 20 min reperfusion) induced a significant increase in blood-to-lumen permeability to FITC-dextran of different molecular weight (10 000, 40 000 and 70 000) without modifying the macroscopic integrity of the gastric mucosa. The increase in vascular permeability was dependent on the time of administration of the tracer and was correlated with an elevation of the protein content of the gastric lumen. Intravenous administration of the secretagogue pentagastrin (20 or 50 $\mu g\,kg^{-1}\,h^{-1}$) did not significantly modify the vascular permeability to dextran in control animals or in animals subjected to haemorrhagic shock. When the intraluminal pH was reduced by intragastric administration of acidic saline solution, only pH 1, which itself induced the appearance of macroscopic mucosal lesions, significantly increased vascular permeability to dextran, both in control animals and in animals subjected to haemorrhagic shock.

These findings suggest that stress induced by haemorrhagic shock increases vascular gastric permeability to dextran, by an acid-independent mechanism, without affecting the macroscopic integrity of the gastric mucosa.

The mucosal membrane is a highly selective physiological barrier, allowing only small quantities of plasma proteins to enter the gastrointestinal lumen. Under experimental (Kusterer et al 1994), pharmacological (Avila et al 1996) and pathological (Kingham et al 1976) conditions the permeability of the mucosa can be significantly increased.

The permeability of capillaries in the gastrointestinal tract has been extensively studied and vascular permeability to macromolecules or plasma proteins is considered to be a functional measure of gastrointestinal mucosal integrity (Granger & Taylor 1980). Thus an increase in gut macromolecular permeability, related to changes in the macroscopic integrity of the mucosa, has been reported in rats after challenge with barrier-breaking agents such ethanol or indomethacin (Melarange & Rashbrook 1987; Kusterer et al 1994; Rusell et al 1995).

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Although haemorrhagic shock is a widely used model for study of acute gastric mucosal injury induced by stress, in most animal models this damage has usually been evaluated by macroscopic and histological techniques after combination with mucosal irritants (Yasue & Guth 1988; Erickson et al 1992). In the current study the gastrolesive effects of stress induced by haemorrhagic shock alone were measured by monitoring changes in the capillary-to-lumen clearance of fluorescein isothiocyanate-labelled dextran (FITC-dextran), a functional measure of gastric vascular permeability (Erickson et al 1992). The macroscopic integrity of the gastric mucosa and the influence of intraluminal pH on stress-induced gastric damage were also evaluated.

Materials and Methods

FITC-dextran and urethane were purchased from Sigma. The reagents needed for the determination of proteins were obtained as a kit from Sigma

Diagnostics (Protein Assay Kit, Procedure P5656). Heparin (Heparina Rovi 5%, Rovi) and pentagastrin (Peptavlon, ICI) were used as preparations available for clinical use.

General

Wistar rats (Charles River, 220–280 g) were fasted overnight but allowed free access to water. Animals were anaesthetized with urethane (1·25 g kg^{-1} i.p.), a femoral vein was cannulated and a tracheotomy was performed to ensure a patent airway. A fine polyethylene tube was inserted into the right carotid artery for monitoring blood pressure (b.p.) and for removal or re-infusion of blood. A soft catheter was inserted into the stomach through an incision in the cervical oesophagus and held in place by a ligature. The abdomen was opened and the duodenum was ligated at a site 1–1·5 cm distal to the pylorus. A tube was passed through an incision in the gastric fundus and the lumen was lavaged gently with warm saline (50–60 mL, 25°C). Temperature was monitored by use of a rectal thermometer (Panlab 0331) and maintained at 36°C by means of an external heat lamp. Blood pressure was determined by means of a pressure transducer (Spectramed Statham P23XL) and a polygraph (Grass model 7). When the blood pressure had stabilized, saline (15 mL kg^{-1}; pH 5·5) was instilled into the stomach via the oesophageal tube. After 20 min blood was withdrawn from the carotid artery, within a 2-min period, into a syringe containing heparinized saline (125 int. units heparin saline mL^{-1}; 0·5 mL). The mean systemic blood pressure was reduced to between 20 and 30 mmHg by the initial bleeding and maintained there for 20 min by additional withdrawal of appropriate volumes of blood when necessary. Thereafter the shed blood was re-infused within a 2-min period and rats received, at different times (0, 5, 10 or 15 min) after the reperfusion period, an intra-arterial injection of FITC-dextran (1·25 μmol kg^{-1} in 0·5 mL saline). The rats were killed by thoracotomy 20 min after blood reperfusion and the stomachs were removed.

Measurement of FITC-dextran blood-to-lumen clearance

FITC-dextran capillary-to-lumen clearance was used as a functional measure of gastric vascular permeability. Preliminary studies were performed to select the MW (Da) of the FITC-dextran used in our studies (10 000, 40 000, 70 000 or 150 000). The different dextrans were administered as equal numbers of molecules. After 1 : 10 dilution in pH 9·26 buffer (preliminary experiments having shown that this pH resulted in maximum fluorescence) the level of FITC-dextran in the gastric contents was measured by spectrofluorimetry (Perkin-Elmer Luminescence Spectrometer LS50) with an excitation wavelength of 495 nm with a 5-nm slit and an emission wavelength of 520 nm with a 10-nm slit. In a further group of experiments the total protein content of the gastric sample was measured by the method of Lowry et al (1951).

Macroscopic evaluation of gastric damage

The stomach was opened along the greater curvature, pinned mucosal side out to a wax block and photographed on colour transparency film. The extent of macroscopically visible damage was calculated from these projected transparencies by computerized planimetry, with the Sigma-Scan program (Jandel Scientific), and gastric injury was expressed as the area (%) of the total gastric mucosa showing macroscopically visible damage.

Influence of luminal pH on stress-induced gastric damage

In a first group of experiments, 20 min before the induction of haemorrhagic shock animals received an intravenous perfusion of pentagastrin (20 or 50 μg kg^{-1} h^{-1}) or saline (pH 7·4). In a second group of experiments the gastric lumen was filled, 20 min before the induction of shock, with 15 mL kg^{-1} saline solution of acidic pH (2·5, 2, 1·5, 1). Gastric acid secretion was determined in samples from the lumen by automatic titration (Radiometer Copenhagen, Denmark) to pH 7 with 0·01 M NaOH. The first sample was collected immediately before the induction of haemorrhagic shock (20 min after the beginning of pentagastrin infusion), and the second at the end of the reperfusion period.

Statistical analysis

All data are expressed as means ± s.e.m. Comparisons between groups of data were performed by means of Student's *t*-test for paired or unpaired data. P values $< 0·05$ were taken as indicative of significance.

Results

Effects of haemorrhagic shock on FITC-dextran blood-to-lumen permeability

In control rats basal permeability to FITC-dextran of MW 10 000 was significantly higher than that to dextrans of a higher MW (Table 1). Haemorrhagic shock significantly increased blood-to-lumen permeability to FITC-dextrans of MW 10 000, 40 000 and 70 000 (263 ± 40%, 198 ± 23% and

Table 1. Capillary-to-lumen clearance of fluorescein isothiocyanate-labelled dextran of different molecular weight in control rats and in rats subjected to haemorrhagic shock (20 min ischaemia + 20 min reperfusion).

Molecular weight of dextran	Clearance (pmol/100 g)	
	Control	Haemorrhagic shock
10 000	65·0 ± 9·6 (n = 4)	1740·0 ± 258·0 (n = 7)*
40 000	24·9 ± 3·7 (n = 26)	49·3 ± 5·6 (n = 26)†
70 000	19·2 ± 3·4 (n = 11)	65·8 ± 21·2 (n = 10)*
150 000	28·5 ± 6·3 (n = 7)	39·0 ± 9·4 (n = 9)

Haemorrhagic shock significantly increased blood-to-lumen permeability to 10 000, 40 000 and 70 000 MW fluorescein isothiocyanate-labelled dextran but failed to modify that to 150 000 MW dextran. The dextran was administered 5 min after the re-infusion of blood. Data are means ± s.e.m. of results from n experiments. * $P < 0.05$, † $P < 0.001$, significantly larger than the value for the respective control group.

343 ± 110%, respectively) but failed to modify permeability to dextran of MW 150 000 (Table 1).

The increase in permeability to MW 40 000 dextran was directly correlated (r = 0·831) with an elevation of protein content in the gastric sample (Figure 1). It was related to the time of administration of the marker, reaching statistical significance only when dextran was re-infused with the shed blood or 5 min after the initiation of the reperfusion period. Administration of dextran at a later stage in the reperfusion period (10 or 15 min) resulted in the absence of a significant increase in the amount found in the gastric lumen (Table 2).

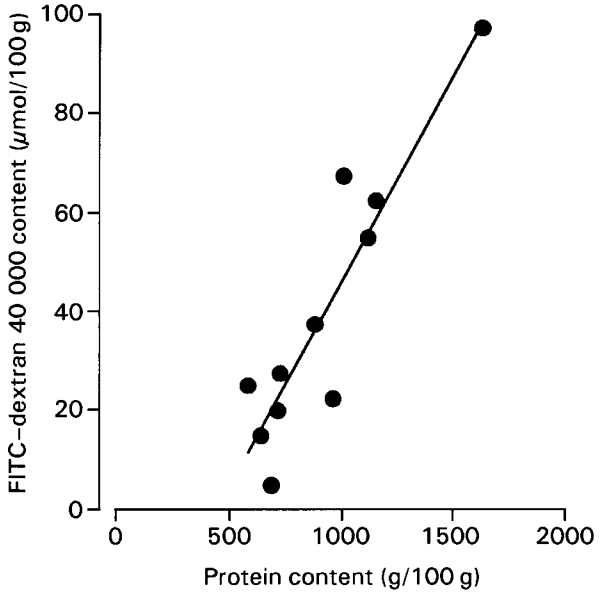

Figure 1. Correlation between total protein and fluorescein isothiocyanate-labelled MW 40 000 dextran (FITC-dextran) contents in the gastric lumen of rats subjected to haemorrhagic shock (20 min ischaemia + 20 min reperfusion).

Influence of the intraluminal acid on stress-induced gastric damage

Haemorrhagic shock induced 66 ± 23% ($P < 0.05$) and 174 ± 57% ($P < 0.01$) increases, respectively, in FITC-dextran blood-to-lumen clearance in animals receiving an intravenous infusion of 20 or 50 $\mu g\,kg^{-1}\,h^{-1}$ pentagastrin compared with that measured in control rats (Table 3). For both doses the blood-to-lumen permeability of FITC-dextran was not significantly different from that resulting from haemorrhagic shock with intravenous infusion of saline (Table 3). Under these experimental conditions the intravenous infusion of pentagastrin (20 or 50 $\mu g\,kg^{-1}\,h^{-1}$) increased the level of acid secretion in control animals but failed to induce such an increase in animals subjected to haemorrhagic shock (Table 4). Higher doses of pentagastrin (100 $\mu g\,kg^{-1}\,h^{-1}$) did not result in a greater increase in gastric acid secretion either in control animals or in rats subjected to haemorrhagic shock.

In a further group of experiments, intragastric administration of acidic saline (pH 2·5, 2 or 1·5;

Table 2. Effects of haemorrhagic shock on capillary-to-lumen clearance of fluorescein isothiocyanate-labelled MW 40 000 dextran in relation to the time of administration of the marker.

Treatment	Time (min)	Clearance (pmol/100 g)
Control	–	28·5 ± 3·0 (n = 64)
Haemorrhagic shock	0	56·8 ± 7·8 (n = 6)*
Haemorrhagic shock	5	47·0 ± 5·5 (n = 26)*
Haemorrhagic shock	10	35·0 ± 3·8 (n = 24)
Haemorrhagic shock	15	23·3 ± 4·5 (n = 12)

Dextran permeability was related to the time of administration of the marker, reaching statistical significance only when dextran was re-infused with the shed blood or 5 min after the initiation of the reperfusion period and not when administered at a later stage (10 and 15 min). Data are means ± s.e.m. of results from n experiments. * $P < 0.01$, significantly different from control result.

Table 3. Effects of intravenous infusion of different doses of pentagastrin or saline on capillary-to-lumen clearance of fluorescein isothiocyanate-labelled 40 000 MW dextran in control rats or rats subjected to haemorrhagic shock.

Dose ($\mu g\,kg^{-1}\,h^{-1}$) of pentagastrin	Clearance (pmol/100 g)	
	Control	Haemorrhagic shock
0	25·9 ± 3·1 (n = 5)	53·1 ± 7·0 (n = 9)†
20	20·8 ± 2·8 (n = 9)	34·5 ± 4·8 (n = 11)*
50	20·3 ± 3·3 (n = 12)	55·5 ± 11·5 (n = 13)†

The blood-to-lumen permeability to fluorescein isothiocyanate-labelled dextran in rats receiving pentagastrin (20 or 50 $\mu g\,kg^{-1}\,h^{-1}$) was not significantly different from that after haemorrhagic shock with intravenous infusion of saline. Data are means ± s.e.m. of results from n experiments. * $P < 0.05$, † $P < 0.01$, significantly greater than respective control result.

15 mL kg^{-1}) did not enhance the effects on permeability to dextran elicited by haemorrhagic shock compared with animals receiving saline at pH 5·5 (Table 5). When the pH of the saline was reduced to 1, blood-to-lumen permeability to FITC-dextran was increased in sham animals, by 205 ± 109% ($P < 0.001$) compared with values for control (pH 5·5) animals (Table 5). Haemorrhagic shock in rats receiving saline at pH 1 induced a 1259 ± 398% increase in the gastric content of FITC-dextran compared with rats with an intraluminal pH of 5·5 (Table 5). Under these conditions the amount of acid in the gastric lumen was substantially reduced 60 min after administration of the acidic saline, both in control animals and in animals exposed to haemorrhagic shock (Table 4).

Effects of haemorrhagic shock on macroscopic gastric damage

Haemorrhagic shock, alone or in combination with intravenous perfusion of pentagastrin, did not affect the macroscopic integrity of the gastric mucosa. When rats received intragastric acidic saline at pH 2·5, 2 or 1·5 the area of the gastric mucosa with damage was less than 1%. When the pH of the saline was reduced to 1, damage in control animals was 12 ± 7% (n = 5) of the gastric area whereas for animals exposed to haemorrhagic shock the damage was 25 ± 11% (n = 7) of the gastric mucosa.

Discussion

In this study FITC-dextran capillary-to-lumen clearance was used as a functional measure of gastric vascular permeability in an experimental model of stress induced by haemorrhagic shock. Reduction of blood pressure to < 30 mmHg for 20 min and re-infusion of the shed blood induced, 20 min later, an increase in vascular permeability to FITC-dextran but did not modify the macroscopic integrity of the gastric mucosa. Previous studies have reported the appearance of macroscopic mucosal damage after use of the same model of stress combined with intragastric administration of mucosal irritants such as exogenous acid (Itoh & Guth 1985; Yasue & Guth 1988) or bile salts (Erickson et al 1992). It is therefore important to point out that our results were obtained in the absence of any such irritants and thus represent changes in blood-to-lumen permeability induced by haemorrhagic shock alone.

Table 4. Acid present ($\mu Eq\,H^+/100\,g$) in the gastric lumen of rats receiving intravenous pentagastrin or intragastric acid saline.

Treatment	Control			Haemorrhagic shock		
	20 min	60 min	n	20 min	60 min	n
Pentagastrin 20 $\mu g\,kg^{-1}\,h^{-1}$	9·9 ± 2·1	25·6 ± 6·2‡	9	9·1 ± 1·1	10·9 ± 1·9	12
Pentagastrin 50 $\mu g\,kg^{-1}\,h^{-1}$	16·4 ± 4·5	35·8 ± 11·7*	10	18·1 ± 3·3	27·1 ± 5·6	16
Saline pH 2·5	4·0 ± 0·5	1·5 ± 0·3‡	8	3·3 ± 0·7	1·8 ± 0·2*	8
Saline pH 2	13·4 ± 2·1	5·2 ± 1·9†	6	11·8 ± 1·8	7·1 ± 2·1‡	10
Saline pH 1·5	26·5 ± 2·5	9·2 ± 1·8‡	7	24·9 ± 2·2	9·7 ± 1·0‡	15
Saline pH 1	63·4 ± 9·9	32·5 ± 11·2	5	86·1 ± 14·2	39·2 ± 6·9†	7

Data are means ± s.e.m. of results from n experiments. * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$, significantly different from the result for the respective 20-min group.

Table 5. Effects of the intragastric administration of saline of different pH on capillary-to-lumen clearance of fluorescein isothiocyanate-labelled 40 000 MW dextran in control rats and in rats subjected to haemorrhagic shock.

pH of saline	Clearance (pmol/100 g)	
	Control	Haemorrhagic shock
5·5	23·0 ± 2·9 (n = 5)	48·0 ± 6·5 (n = 8)†
2·5	18·3 ± 4·0 (n = 8)	39·0 ± 7·8 (n = 8)*
2·0	10·5 ± 1·5 (n = 5)	48·3 ± 12·0 (n = 10)*
1·5	18·8 ± 3·3 (n = 8)	59·0 ± 12·8 (n = 14)*
1·0	71·0 ± 25·3 (n = 5)‡	965·0 ± 282·5 (n = 7)*‡

Intragastric administration of acidic saline at pH 2·5, 2 or 1·5 did not enhance the effects on permeability to dextran elicited by haemorrhagic shock in animals receiving saline at pH 5·5. A significant increase in blood-to-lumen permeability of fluorescein isothiocyanate-labelled dextran was observed for rats in both sham or haemorrhagic shock groups receiving pH 1 saline compared with rats in the same groups receiving pH 5·5 saline. Data are means ± s.e.m. of results from n experiments. * $P < 0·05$, † $P < 0·01$, significantly different from result for respective control group; ‡ $P < 0·05$, significantly different from result for respective saline at pH 5·5.

The increase in vascular permeability was related to the MW of the dextran. Thus MW 10 000 dextran spontaneously leaked from the microvasculature to the gastric lumen under basal conditions whereas the amount of leakage of dextrans of higher MW was lower. Haemorrhagic shock induced a substantial increase in vascular permeability to 10 000, 40 000 and 70 000 MW dextran, suggesting that globulins or proteins such as albumin will be present in the gastric lumen of rats subjected to haemorrhagic shock. Furthermore, the amount of MW 40 000 FITC-dextran in the gastric lumen was correlated with an elevation of protein content.

The administration of FITC-dextran immediately before reperfusion generates a greater increase in blood-to-lumen leakage of this marker. Because this could be the consequence of an increase in local hydrostatic pressure (Bayati 1990) we excluded such a procedure to avoid the possibility that the permeability changes were induced by the increase in blood pressure that follows restitution of the blood, rather than being induced by the gastric mucosal injury. FITC-dextran was administered 5 min after the initiation of the reperfusion period, when the arterial blood pressure reached values similar to those under basal conditions. The administration of dextran at a later stage in this period failed to induce a significant increase in the amount found in the gastric lumen. This observation might be because of rapid formation of a mucoid cap of mucus and cell debris that, combined with the speed of the restitution process, forms a barrier preventing mixing of the gastric contents with the different substances and cells extravasated from blood vessels (Wallace 1989; Wallace & McKnight 1990).

Previous studies have reported a marked aggravating effect of acid on gross and histological mucosal injury in a haemorrhagic shock model (Yasue & Guth 1988). Although in the current study intravenous infusion of maximum doses of the secretagogue pentagastrin did not modify the increase in vascular permeability induced by haemorrhagic shock, under these conditions measurement of intragastric pH showed no increase in luminal acid in animals subjected to the shock. To ensure low pH in the gastric lumen animals received intragastric administration of acid saline. Low values of intraluminal pH (e.g. 1·5) did not induce the appearance of greater amounts of dextran in the gastric lumen, suggesting that the increase in vascular permeability induced by haemorrhagic shock is independent of the amount of acid present in the gastric lumen. Only values of intraluminal pH = 1, which by itself increased vascular permeability to dextran and provoked macroscopic damage, significantly enhanced microvascular and gastric mucosal damage induced by haemorrhagic shock.

An increase in acid back-diffusion by different noxious agents has been reported (Lau et al 1992; Lippe & Holzer 1992). In the current study, the amount of acid exogenously administered in the gastric lumen diminishes significantly 60 min after administration. However, this diminution is similar in controls and animals subjected to haemorrhagic shock, suggesting that it is not the haemorrhagic shock itself but rather intraluminal acidity (Kiviluoto et al 1988) that is responsible for the acid back-diffusion observed under these experimental conditions. Taking this into account, the failure of pentagastrin to increase the amount of acid in the gastric lumen after haemorrhagic shock is more likely to be because of inhibition of gastric acid secretion than neutralization or diminution of the amount of intraluminal acid when it has been secreted. Recent studies by our group have demonstrated stress-associated activation of an inhibitory reflex mechanism on gastric acid secretion, mediated by synthesis of nitric oxide, in the brain (Martínez-Cuesta et al 1992; Barrachina et al 1995; Esplugues et al 1996). However, the reduction in gastric mucosal blood flow in response to haemorrhagic shock could also be involved in the failure of pentagastrin to increase gastric acid secretion in those circumstances (Tepperman & Jacobson 1994).

In summary, these results show that stress induced by haemorrhagic shock increases dextran

vascular gastric permeability without affecting the macroscopic integrity of the gastric mucosa. This indicates a discrepancy between the pathogenesis of damage to the superficial epithelium and the mucosal vasculature, with functional changes being apparent before macroscopic changes can be demonstrated. This damage is independent of the level of acid in the gastric lumen and only levels of intraluminal pH = 1, that by itself induced macroscopic damage, significantly increased vascular permeability to dextran in rats subjected to haemorrhagic shock.

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