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ACUTE GASTRIC EROSIONS IN THE RAT

I. Microangiography

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The local or systemic administration of non-steroid anti-inflammatory drugs (NSAID) to fasting rats induces, in the presence of acid secretion, acute superficial necrotic lesions in the gastric mucosa (ROBERT 1977). The mechanism(s) by which these erosive lesions are induced remain unknown (MILLER & JACOBSON 1979). It may be speculated, however, that one or several of the following mechanisms may contribute to the mucosal erosions induced by NSAID:

(1) By inducing local disturbance of the vessels nourishing the gastric mucosa (i.e. ischaemic erosions). MAIN & WHITTLE (1975) demonstrated a reduction of the gastric mucosal flow after indomethacin treatment in the rat.

(2) By lumen-borne injury of the superficial gastric cells, without disturbance of the mucus-barrier. A high concentration of aspirin was found after oral administration in certain of the gastric mucosa in the rat (RAINSFORD 1975). Since aspirin is known to inhibit prostaglandin synthesis, it is possible that local deficiency of prostaglandins (necessary for the normal integrity of the cells; ROBERT et coll. 1979) may induce local injury to the gastric mucosa.

(3) By blood-borne toxicity, resulting in decreased local cellular trophism in the gastric mucosa (i.e. blood-borne cytotoxic erosions). DJAHANGUIRI (1969) and ROBERT et coll. have demonstrated that NSAID may induce superficial gastric erosions in the rat also after intraperitoneal or subcutaneous administration. Whether circulating NSAID, partly excreted into the gastric lumen, is able to induce lumen-borne erosions remains unknown.

(4) By local disturbance of the components of the mucus protecting the superficial gastric cells (spotty insufficiency of the mucus-barrier).

In the present work the first hypothesis, that mucosal erosions are induced by an ischaemic mechanism, was investigated.

Material and Methods

Sixteen adult male Sprague-Dawley rats, weighing about 200 g, were used. The rats were kept fasting for 24 h in specially devised cages (ROBERT & ASANO 1977).

Thirty mg of indomethacin/kg body weight, dissolved in 2 ml vehicle were administered by intragastric instillation through a semirigid plastic tube to 8 rats. The tip of the tube was smoothened in order to avoid injury to the oesophageal or gastric mucosa. The same dose of indomethacin was given subcutaneously to 3 rats. The remaining 5 rats received 2 ml vehicle, 3 by intragastric instillation and 2 through subcutaneous injection.

Laparotomy was performed under either anaesthesia 5 h after the administration of indomethacin. After thoractomy, a needle (6 gauge) adapted to a

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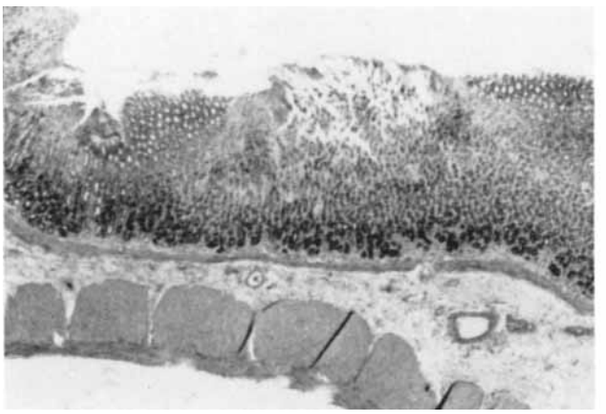

Fig. 1. Gastric mucosa of a rat, 5 h after subcutaneous administration of indomethacin. Superficial erosions (H & E, ×20).

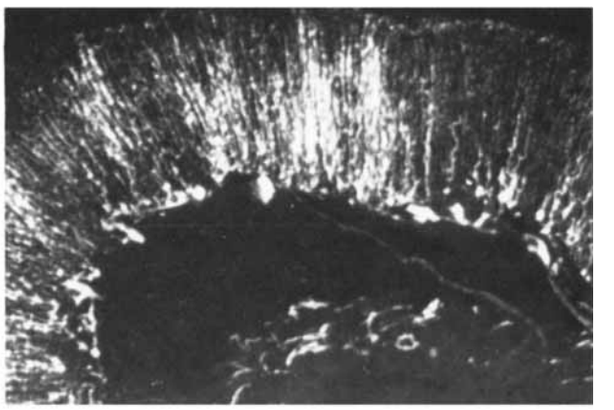

Fig. 2a

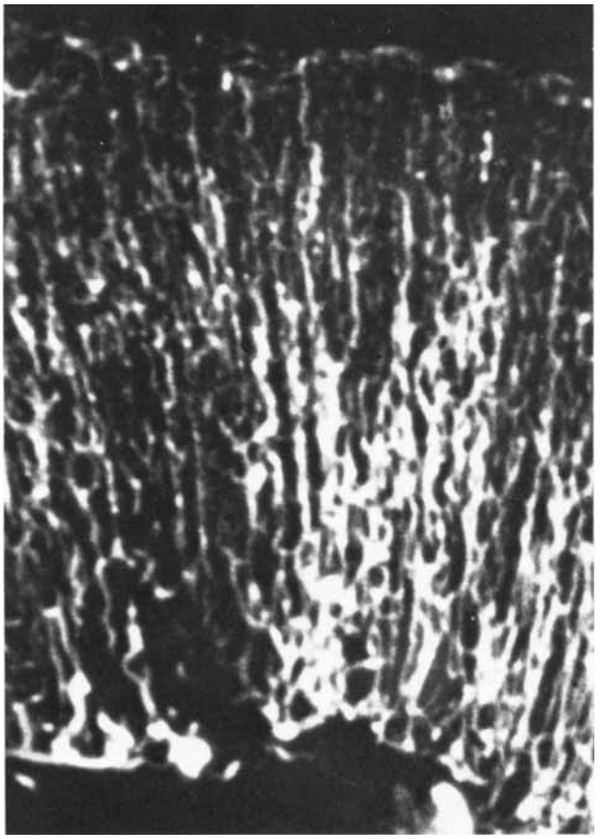

Fig. 2b

Fig. 2. a) Microangiography of the gastric mucosa of a rat treated as in Fig. 1. Vertical intramucosal vessels as well as interlacing vessel at the luminal border (Micropaque, ×20). b) Detail of (a) to demonstrate the intramucosal anastomotic capillaries as well as the even luminal border on top (Micropaque, ×260).

tube, connected to a manometer, was introduced into the ventral aspect of the thoracic aorta.

The proximal, abdominal vena cava was cut and the vascular system was perfused through the aorta with saline under monometric control (up to 160 mmHg) until saline poured out of the distal part of the inferior vena cava. The vascular system was perfused through the same cannula with a fine 0.5 per cent suspension of Micropaque, which was injected slowly under manometric control (not exceeding 160 mmHg; LJUNGQVIST 1962). When the Micropaque poured out of the distal part of the inferior vena cava, the perfusion was stopped. All gastrointestinal organs were removed. The oesophagus, the transverse colon and about 2 cm of the jejunum as well as the stomach were cut wide open and pinned onto cork plates. After fixation in formalin, the preparations were embedded in paraffin.

Sections (200 μm thick) were cut and subsequently placed on Kodak maximum resolution plates. The plates were exposed with 8 mA; exposure time 4 h. The exposed blocks were re-embedded in paraffin after which 6 μm thick sections were cut for microscopic examination (H & E stain).

Morphometric determinations. The number of vessels in the corpus were registered in defined areas by the aid of an ocular scale which covered 1.8 mm×0.8 mm of the preparation. Ten consecutive areas were examined in both vehicle treated and indomethacin treated animals. In the latter group of animals, determinations were carried out both in 10 areas beneath ulcerations and in 10 areas without ulcerations.

The transversal diameter of 20 consecutive verti-

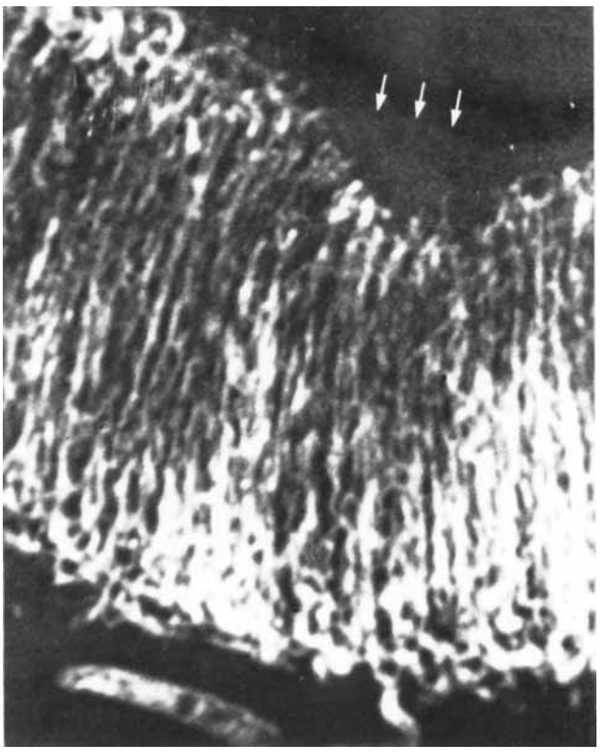

Fig. 3. Microangiography of the gastric mucosa of a rat treated as in Fig. 1. Normal distribution of vessels beneath the gastric erosion (→; Micropaque, ×260).

cal intramucosal vessels were registered in the corpus mucosa in vehicle treated and indomethacin treated animals (both in areas beneath ulcerations and areas without ulcerations). Measurements were made in the mid-portion of the mucosa in all animals.

Results

Macroscopic findings. Five hours after intragastric instillation or subcutaneous injection of indomethacin, several (up to 20) circumscribed erosions were observed (KOLLBERG & JOHANSSON, personal communication). These erosions were located in the corpus, i.e. the part of the stomach secreting acid and pepsin, and usually occurred on top of mucosal folds. Erosions were seldom observed in the antrum or in the forestomach.

Microscopic findings. Mucosal erosions appeared as circumscribed defects in the superficial third of the glands. The material within the erosive lesions was composed of necrotic cells, blood and fibrin. Glandular cells surrounding the erosions were apparently intact (Fig. 1). Lesions involving the full thickness of the mucosa were not observed. No lesions were found in vehicle treated controls.

Microangiographic findings. The normal gastric mucosa in vehicle treated animals had one to two submucosal vessels, parallel to the luminal border. At right angles to these vessels, smaller relatively tightly packed vessels were observed in the lamina propria. At some points, the horizontal (submucosal) and perpendicular (lamina propria) vessles communicated. The smaller perpendicular vessels in the lamina propria communicated with each other at various mucosal levels by an interlacing capillary network. At the luminal surface, slender capillaries anastomosed perpendicular mucosal vessels. Nonerosive mucosa of indomethacin treated animals had the same appearance (Fig. 2).

The vascularity underneath gastric mucosal erosions of indomethacin treated animals was similar to that described for vehicle treated controls. However, at the place of mucosal erosion the perpendicular vessels in the lamina propria ended abruptly. This may explain the haemorrhage usually found covering gastric erosions. The terminal capillary anastomoses found near the luminal border both in normal gastric mucosa of vehicle treated and of indomethacin treated animals was not present in the mucosa underneath the eroded areas (Fig. 3).

A mean of 5 vessels/defined area of lamina propria (range 4 to 6) was recorded in normal mucosa in 16 rats (both in vehicle and in indomethacin treated). The same number of vessels/area of lamina propria was recorded for mucosa adjacent to indomethacin induced erosions.

Micrometric determinations of normal mucosa in vehicle treated and indomethacin treated animals (including normal-looking mucosa and mucosa surrounding erosions) indicated that the mean diameter of the horizontal vessels of the submucosa was 8 μm (range 6 to 9). The vertical vessels measured 3 μm (range 2 to 4). The difference was not significant in the various groups (including intragastric or subcutaneous indomethacin administration).

The intragastric or subcutaneous administration of indomethacin induced no difference in the microangiographic appearance.

Discussion

The present results have demonstrated that the gastric mucosa of vehicle treated animals contains

regular, small perpendicular vessels that nourish the mucosa. This mode of vascularity was found in the glandular part of the stomach (body and antrum). These results are in accordance with the description of the vascular distribution in the normal rat given by NYLANDER & OLERUD (1960, 1961).

The intact mucosa and the mucosa surrounding erosions had the same appearance in indomethacin treated animals as in vehicle treated ones.

The normal vessels in the mucosa reached the luminal border of the epithelium and there interlaced with a terminal intercommunicating vessel. This latter vessel was absent underneath gastric erosions.

Quantitative analysis indicated that the number of intramucosal vessels/area and their size were similar both in normal mucosa of vehicle treated and indomethacin treated animals (including areas surrounding glandular erosions). The absence of vascular dilatation underneath those mucosal lesions seems to indicate that gastric erosions are not induced by injury to the vascular system in the mucosa; otherwise proximal vascular dilatation following protracted spasm of microthrombosis would have been evident.

MAIN & WHITTLE (1975) demonstrated by another technique that the mucosal blood flow diminished following parenteral administration of indomethacin. Their results, however, differed from those of NYLANDER & OLERUD (1961). On the contrary, the administration of aspirin (also from the NSAID family) has been shown to increase the gastric mucosal blood flow in the rat (MOGÅRD, personal communication). Thus, the experiments with blood flow analysis appear at present to be contradictory and therefore inconclusive. That technique does, however, not permit identification of vessels engaged in the process of blood flow derangement and their topographic localization in the stomach (mucosal or submucosal). Therefore, microangiography appears to be a more specific method to investigate the minute vessels of the normal gastric mucosa, including those surrounding gastric erosions.

Since similar results were found by intragastric or by subcutaneous administration of indomethacin, it appears that circulating indomethacin excreted into the gastric lumen is able to induce lumen-borne erosions.

In conclusion, it was found that the anatomy of the vascular gastric intramucosal system in the rat is not influenced, neither by intragastric nor by subcutaneous administration of indomethacin. Thus, gastric erosions appear to be induced by mechanisms other than by vascular injury. The possibilities that mucosal erosions induced by indomethacin mirror direct cell toxicity by the drug or decreased cell protection by hampered prostaglandin production are being investigated at this laboratory.

SUMMARY

Microangiography of the gastric mucosa was performed in 16 adult rats 5 hours after administration of indomethacin. Superficial gastric erosions were induced irrespective of the route of administration. Microangiography demonstrated absence of vascular dilatation underneath the superficial gastric erosions, suggesting absence of protracted vascular spasm or microthrombosis in eroded areas. The presence of normal microangiographic appearances underneath the gastric erosions suggests that such lesions may be induced by mechanisms other than by vascular injury.

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