Prostaglandin E1 and a Serine Protease Inhibitor Protect the Gastric Microcirculation and Increase the Gastric Acid Secretion After Thermal Injury

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Key words. Prostaglandin E1, Serine protease inhibitor, Gastric acid, Gastric microcirculation

Microcirculatory disturbance of the gastric wall is a crucial factor in the development of gastric mucosal lesions induced by Helicobacter pylori [1–3], anti-inflammatory drugs [4,5], and stress [6,7]. After thermal injury to the dorsal skin in rats, macroscopic hemorrhagic erosion developed in 14.3% at 15 min, 42.9% at 2 h, 100% at 5 h, and 85.7% at 12 h [8]. Macroscopic hemorrhagic erosion is formed within 5 h after thermal injury. Under the stereoscopic microscope, superficial gastric erosion could be observed in all rats studied at 15 min. Gastric mucosal blood flow decreased at 15 min, partially improved at 2 h, and decreased again at 5 h after thermal injury [9]. Since the blood flow was depressed especially at 15 min and 5 h, we have investigated mechanisms of the decrease in gastric mucosal blood flow at 15 min and 5 h. Silicon rubber casts of the vasculature revealed contraction of arterioles 15 min after thermal injury to the dorsal skin in the rat model [10]. We also observed the gastric microvessels by in vivo microscopy which was first described by Guth and

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Rosenberg [11,12]. In vivo microscopic observation of gastric microcirculation showed also the contraction of arterioles 15 min after thermal injury [13]. The contraction can be responsible for the decrease in gastric mucosal blood flow 15 min after thermal injury. Five hours after thermal injury, in vivo microscopy showed irregular constriction of the venules caused by suppressed production of nitric oxide [14]. The addition of leukocytes stimulated by phorbol myristate acetate to the endothelial cell monolayer caused a significant increase in the intracellular peroxide level in the endothelial cells and severe endothelial cell injury after 5 h, thus suggesting the presence of leukocyte-dependent endothelial damage [15].

Rats in the prostaglandin E1 (PGE1) group were administered 1.0 μg/kg per minute intravenously from 30 min before thermal injury. Microvascular images in the basal region of the gastric mucosa were observed by in vivo microscopy, and carboxyfluorescein diacetate succinimidyl ester dependent leukocyte illumination was monitored. Monastral blue B (MBB) was administered intravenously and deposits of MBB in venules were observed. Diameters of arterioles and accompanied venules were measured and arteriolar diameter/venular diameter (A/V ratio) was calculated at three different points. The gastric effluent was perfused (10 ml/h), and was collected every 1 h. The percentage of rolling leukocytes was significantly higher in rats at 2 h after injury than that in the normal control group, and significantly lower in the PGE1 group than that in the saline-administered group. Percentage of the MBB deposits area was significantly higher in the 2 h after injury group than that in the normal control group, and significantly lower in the PGE1 group than that in the saline-administered group. A/V ratio in the 2 h group was significantly smaller than that in the normal control group. In the PGE1 group, gastric mucosal lesion was suppressed, and rolling of leukocyte and area of MBB deposits were inhibited. One hour after thermal injury, gastric acid secretion was increased in the PGE1 group.

A serine protease inhibitor, camostat mesilate (CM) (100 mg/kg), was administered i.g. 30 min before thermal injury. In the CM group, gastric mucosal lesion was suppressed, and rolling of leukocyte and area of MBB deposits were inhibited. Before thermal injury, CM did not affect gastric acid secretion. After thermal injury, gastric acid secretion was decreased in the distilled water-administered rats and was increased in the CM group (Fig. 1).

Gastric acid secretion is increased in animal experimental models of stress. However, a rapid decrease in the gastric mucosal blood flow, energy charge depression, damage to the mitochondria in parietal cells, parietal resting stage, and low acid output were observed after thermal injury [16]. It was hypothesized that microcirculatory disturbance was the cause of the low acid output after thermal injury. It is suggested that CM and PGE1 inhibit gastric mucosal lesion at least in part by protection against microcirculatory distur-