Cytoprotective Effect of Plasmin Inhibitor on Necrotizing Agent-Induced Gastric Lesions in Rats

Motonobu MURAKAMI, Jung Keun YOO, Sanae TERAMURA, Masami INADA, Hiroshi SAITA, Keiji MATSUO, Sigeru KUSAKA, Toru KITA and Takeo MIYAKE

Department of Geriatric Medicine, Faculty of Medicine, Kyoto University, Kyoto 606, Japan
1 Kyoto National Hospital, Kyoto 612, Japan

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Abstract—We studied the effect of plasmin inhibitor on ethanol and ammonia-induced gastric mucosal lesions in rats using an ex vivo chamber. Tranexamic acid and aminocaproic acid significantly inhibited macroscopic gastric hemorrhagic necrosis and attenuated the decrease of gastric transmucosal potential difference induced by 50% ethanol and 1% ammonia. The protection of gastric mucosa afforded by tranexamic acid and aminocaproic acid was not affected by pretreatment with indomethacin (5 mg/kg). These results suggest that plasmin inhibitor plays an important role in the prevention of gastric deep necrosis following exposure of the stomach to a damaging agent.

The term “cytoprotection” is the property to protect gastric mucosal tissue located under the surface epithelium from becoming necrotic after exposure to necrotizing agents (1, 2). It is suggested that fibrinolysis plays a role in the pathogenesis of tissue injury (3). Plasmin is a proteolytic enzyme that has specific affinity to fibrinogen and fibrin, and fibrinolytic activity in the stomach has been demonstrated (4). We therefore studied the effect of plasmin inhibitor (tranexamic acid and aminocaproic acid) on rat gastric mucosal lesions induced by necrotizing agents.

Male Sprague Dawley rats weighing 220 g were used. The rats were anesthetized with urethane (1 g/kg, i.m.), and an ex vivo gastric chamber was prepared (5). In the control group, the chamber was instilled with 2 ml of saline for 15 min; and subsequently, 2 ml of 50% ethanol or 1% ammonia was placed in the chamber for 5 min. The chamber was then rinsed and filled with saline again and replaced every 15 min for 1 hr. In the test group, the gastric mucosa was exposed to 2 ml of 1, 5 or 10% (w/v) tranexamic acid (Daiichi Pharm Co., Tokyo) or aminocaproic acid (Nacalai Tesque NIC., Kyoto) dissolved in distilled water for 15 min before instillation of 50% ethanol and 1% ammonia. To investigate alteration of the gastric mucosal integrity, we measured transmucosal potential difference (PD) continuously before and after exposure of the stomach to ethanol and ammonia. Animals were killed at the end of the experiment, and the stomach was examined for macroscopic hemorrhagic lesions under a dissecting microscope (×10). The area of each lesion (mm²) was measured, and the summation of the area was regarded as the lesion index (LI). For microscopic study, the stomach was immersed in 10% formalin and processed for routine light microscopy. Statistic analysis was performed by Student’s t-test.

In the resting state, gastric mucosa in the chamber produced stable transmucosal PD. In the control group, after exposure to 50% ethanol and 1% ammonia, the decreases of transmucosal PD were by 52% and 79%, respectively; and severe macroscopic hemorrhagic lesions were observed. Pretreatment with 2 ml of 1, 5 and 10% tranexamic acid or aminocaproic acid significantly inhibited both the decrease in transmucosal PD and for-
formation of macroscopic lesions induced by 50% ethanol and 1% ammonia, respectively, in a concentration-dependent manner (Table 1 and Fig. 1). Histological examination revealed that pretreatment with tranexamic acid and aminocaproic acid inhibited deep

Table 1. Effect of 50% ethanol and 1% ammonia on gastric transmucosal potential difference (PD, mV) of tranexamic acid and aminocaproic acid-treated rats

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Ethanol</th>
<th>Ammonia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>60 min</td>
</tr>
<tr>
<td>TA (5%)</td>
<td>37.6±2.6</td>
<td>32.4±1.8* (86%)</td>
</tr>
<tr>
<td>TA (10%)</td>
<td>36.7±5.0</td>
<td>31.0±7.7* (84%)</td>
</tr>
<tr>
<td>IND+TA (10%)</td>
<td>39.6±1.6</td>
<td>31.8±7.4* (80%)</td>
</tr>
<tr>
<td>IND</td>
<td>32.8±3.7</td>
<td>17.6±8.2 (54%)</td>
</tr>
<tr>
<td>Control</td>
<td>33.0±3.7</td>
<td>16.0±6.1 (48%)</td>
</tr>
<tr>
<td>ACA (5%)</td>
<td>38.6±6.7</td>
<td>25.8±7.9* (67%)</td>
</tr>
<tr>
<td>ACA (10%)</td>
<td>38.6±2.8</td>
<td>32.4±8.8* (84%)</td>
</tr>
<tr>
<td>IND+ACA (10%)</td>
<td>39.2±4.1</td>
<td>32.6±7.9* (83%)</td>
</tr>
</tbody>
</table>

*p<0.05, compared to the saline control. TA: tranexamic acid, ACA: aminocaproic acid, IND: indomethacin. Indomethacin (5 mg/kg) was given subcutaneously 45 min before administration of TA and ACA. n=5, (Mean±S.D.).

Fig. 1. Effects of tranexamic acid (TA 10%) and 6-aminocaproic acid (ACA 10%) on 50% ethanol and 1% ammonia-induced gastric lesions. Lesion indexes were significantly decreased by tranexamic acid (TA) and 6-aminocaproic acid (ACA). The protective effects of TA and ACA against ethanol and ammonia-induced lesions were not reversed by pretreatment with indomethacin (IND, 5 mg/kg, s.c.). n=5, (Mean±S.E.).
necrosis induced by 50% ethanol and 1% ammonia, respectively. The protection against macroscopic lesions and inhibition of the decrease in transmucosal PD afforded by them were not affected by pretreatment with indomethacin (5 mg/kg) (Fig. 1).

Tranexamic acid and aminocaproic acid are potent antifibrinolytic drugs. Tranexamic acid has been reported to have inhibitory effects on hemorrhage after prostatic surgery (6), menorrhagia (7), and gastrointestinal bleeding (8). It is also reported that intravenous administration of tranexamic acid significantly decreased the volume of gastrointestinal bleeding in humans (8). However, there is no study concerning the gastric cytoprotective effect of plasmin inhibitor.

In this study, we demonstrated that tranexamic acid and aminocaproic acid inhibited gastric mucosal necrosis induced by necrotizing agents. This protective effect of plasmin inhibitors was not affected by the pretreatment with indomethacin, suggesting that the protection is independent of the action of endogenous prostaglandins. We previously reported that exogenous 16,16-dmPGE2 had a protective effect against ethanol-induced gastric lesions, but not against ammonia-induced lesions in rats (9). In contrast, the present study clearly demonstrated that plasmin inhibitor markedly protected the gastric mucosa against both ammonia and ethanol. These studies show that plasmin inhibitor per se has cytoprotective action and suggest that plasmin activity plays an important role in the development of gastric mucosal damage.

References