EFFECT OF PROSTAGLANDINS ON MUCOSAL BLOOD FLOW AND ASPIRIN-INDUCED DAMAGE IN THE CANINE STOMACH

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Abstract—This study deals with the action in anesthetized dogs of prostaglandin E2 and F2α given into the celiac artery and the femoral vein on gastric mucosal blood flow and on gastric mucosal damage induced by aspirin. In the non-stimulated stomach, infusion of prostaglandin E2 or F2α into the celiac artery resulted in a marked increase in mucosal blood flow and a sustained decrease, respectively. In contrast, an infusion of prostaglandin E2 into the femoral vein produced a decrease in mucosal blood flow, whereas prostaglandin F2α produced a biphasic response: a transient increase followed by a decrease. It was observed that intravenously infused prostaglandin E2, while reducing mucosal blood flow, significantly diminished mucosal lesions, altered transmucosal potential differences and H+ back-diffusion induced by a topical application of aspirin. The findings indicate that the action of prostaglandins on gastric mucosal blood flow alters depending on the route of administration and that prostaglandins seem to exert gastric cytoprotection through mechanisms other than an increase in mucosal blood flow.

In recent years, practically every type of prostaglandin (A, B, C, D, E, F, and I) has been shown to be cytoprotective against the effects of noxious agents on the gastrointestinal mucosa (1). Several mechanisms of cytoprotection have been proposed, but an exact one has not yet been established. Some investigators postulated that cytoprotection by prostaglandins (PGs) might be mediated through an increase in mucosal blood flow (2–4). The possibility that PGs exert cytoprotection through changes in gastric mucosal blood flow (GMBF) is controversial, as the action of PGs on vascular beds differs with each type, i.e., PGE2 is a peripheral vasodilator and PGF2α is a vasoconstrictor. Although the effect of PGE2 on gastric mucosal blood flow has been reported, the results are not consistent (2, 5–8). On the other hand, the effect of PGF2α on GMBF has not been established clearly.

In this study, we attempted to clarify the actions of PGE2 and PGF2α on GMBF in anesthetized dogs by two routes of administration, the celiac artery and the femoral vein, because discrepancies in the effect of PGs on GMBF reported so far might be due to differences in the route of administration. Furthermore, the effect of i.v. infused PGE2 on aspirin-induced gastric mucosal damage was studied to elucidate whether the increase in mucosal blood flow is necessary for cytoprotection.

Materials and Methods

Animals and procedures: Mongrel dogs of either sex weighing between 7.0–19.0 kg were fasted for 18 hr and anesthetized with pentobarbital Na (30 mg/kg, i.v.). The trachea was cannulated and the abdomen opened. A catheter was introduced into the stomach via the pylorus through an incision.
in the duodenum; the pylorus was then ligated. Polyethylene tubes (ED 1.2 mm) for infusion of aminopyrine and the drugs or for blood sampling were placed in the superficial vein in one foreleg and in both femoral veins. For the intra-arterial administration of drugs, a Teflon tube (ED 1.5 mm, ID 1 mm) cannulated from the left femoral artery was retrogradely led into the celiac artery and fixed in the left femoral artery. In the intravenous route, drugs were given into the left femoral vein.

**Gastric mucosal blood flow (GMBF):**
GMBF was measured in anesthetized dogs according to the method of Jacobson et al. (9). Aminopyrine dissolved in physiological saline was given intravenously in a loading dose of 20 mg/kg, followed by a maintenance dose of 5 mg/kg/hr throughout each experiment. A 2 hr equilibration period was allowed before each study began; during this time, the stomach was irrigated with an acid solution composed of 100 mM HCl and 50 mM NaCl. One hundred ml of the acid solution warmed at 37°C was instilled into the stomach and recovered 15 min later. This procedure was repeated at 15 min intervals. Blood samples were drawn from the right femoral vein every 1 hr, and plasma was obtained. The concentration of aminopyrine in the acid solution recovered from the stomach or the plasma samples was determined by the method of Brodie and Axelrod (10). Aminopyrine clearance was calculated from the formula used by Jacobson et al. (9) to measure mucosal blood flow. The mean GMBF during the initial 60 min was designated as 100%. The GMBF during each period was expressed as a percentage of this basal flow rate.

**Intra-arterial (i.a.) or intravenous (i.v.) administration of drugs was scheduled as follows:** i.a. infusions of saline for 1 hr and of PGE₂ or PGF₂α for the next 1 hr were given. Saline was then infused for 1 hr to observe the recovery from the effect of PGE₂ or PGF₂α. Thereafter, β-isoproterenol or papaverine was infused for 30 min. The schedule of i.v. infusion of drugs was identical to that in the i.a. infusion, except for the doses.

**Blood pressure and heart rate were recorded on a polygraph** (Nihon Kohden, RM-150) using a pressure transducer (Nihon Kohden, RP-3) and a tachometer (Nihon Kohden, RT-2) connected to the cannula placed in the right femoral artery.

**Aspirin-induced gastric mucosal damage:**
As in the study of GMBF, the experiment was started after an equilibration that followed aminopyrine dosing. The study was separated into four 30 min periods. In periods I, II, and IV, the stomach was filled with 100 mM HCl, 15 mM NaCl, 78 mM mannitol, and 40 mg/l phenol red. In period III, the same solution with 5 mg/ml aspirin added was instilled. During each period, exactly 110 ml of the solution was instilled into the stomach, and 10 ml immediately removed. Thirty minutes later, the solution instilled into the stomach was carefully aspirated off, and the two aspirates were analyzed for H⁺, Na⁺ and phenol red concentration. The H⁺ concentration was determined by titration to pH 7.0 using an automatic titrator (Radiometer, Copenhagen). The Na⁺ concentration was measured on a flame photometer with an automatic diluter (Hitachi, 205D). Phenol red concentration was measured by the method of Hunt and Knox (11) and used as a dilution indicator. The net flux of each ion was calculated by subtracting the instilled amount of ion from the recovered amount. The recovered acid solution and the plasma obtained hourly were also analyzed for aspirin concentration. Aminopyrine clearance in each period was calculated from the formula. The GMBF in period I was designated as 100% (basal flow rate), and that in each period was expressed as a
percentage of the basal flow rate. In the control group, saline was infused i.v. at a rate of 2.5 ml/hr throughout each period. In the PGE2 group, PGE2 was infused i.v. at 1 μg/kg/min during periods II, III, and IV. At the end of period IV, the dog was killed, and the stomach removed and filled with 10% formalin solution for fixation. Ten minutes later, the stomach was incised along the greater curvature and examined for lesions. The area (mm²) of each lesion was measured, summed, and used as a lesion index.

In this study, electrical potential difference (PD) was measured as follows: A polyethylene catheter filled with 3% agar in saturated KCl was introduced into the stomach through the pylorus, and a reference catheter filled with agar and KCI was placed in the peritoneal cavity. Each electrode led to a separate beaker filled with saturated KCl in which a balanced calomel electrode was placed and in turn connected to a DC microvolt ammeter (Toa Electronics Ltd., PM-18C). The change in PD was measured, and the mean of the values read every 5 min throughout each period was calculated.

Drugs: Drugs used in this study were aminopyrine (Yashiro Seiyaku), PGE2 (Fuji Chemical), PGF2α (Fuji Chemical), /-isoproterenol hydrochloride (Nikken Kagaku), papaverine hydrochloride (Hoei Yakuko), and aspirin (Yoshitomi).

Statistics: Results are shown as the mean±standard error. Statistical significance was determined by Student’s t-test.

Results
Effects of PGE2 and PGF2α infused into the celiac artery on GMBF

The basal GMBF in anesthetized dogs was 13.6±1.3 ml/min (n=30). Saline infusion by i.a. and i.v. produced no significant change in GMBF throughout the experiments.

1. PGE2: Infusion of PGE2 into the celiac artery produced a dose-dependent increase in GMBF: PGE2 in doses of 0.1 and 0.2 μg/kg/min increased GMBF by 78.0% (n=2) and 127.5±25.0% (n=5) at peak, respectively. The pattern of responses in GMBF, diastolic blood pressure (BP), and heart rate (HR) caused by i.a. infusion of PGE2 (0.2 μg/kg/min) and /-isoproterenol (0.1 μg/kg/min) is shown in Fig. 1. The increase in GMBF is evident within 15 min of the beginning of PGE2 infusion, and the GMBF returned to almost the basal level within 1 hr after the infusion was stopped. /-Isoproterenol significantly increased GMBF. Intra-arterial infusion of PGE2 and /-isoproterenol produced no significant alterations in BP and

![Fig. 1. Effects of PGE2 and /-isoproterenol infused into the celiac artery on gastric mucosal blood flow (GMBF), heart rate (HR) and diastolic blood pressure (BP) in anesthetized dogs. Results expressed as the mean±S.E. of five dogs. **P<0.01, ***P<0.001 as compared to the value obtained just prior to PGE2 administration. P<0.05 as compared to the value obtained during 15 min before /-isoproterenol administration.](image-url)
PGF$_2\alpha$: Infusion of PGF$_2\alpha$ into the celiac artery in a dose of 0.2 $\mu$g/kg/min produced a gradual but significant decrease in GMBF (Fig. 2). The reduction continued for at least 1 hr after the infusion was stopped. Papaverine (0.1 mg/kg/min, i.a.) produced a slight but not significant increase in GMBF. PGF$_2\alpha$ and papaverine given into the celiac artery produced no significant changes in BP and HR.

**Effects of PGE$_2$ and PGF$_2\alpha$ infused into the femoral vein on GMBF**

1. PGE$_2$: Infusion of PGE$_2$ in a dose of 0.02 $\mu$g/kg/min into the femoral vein did not affect GMBF. PGE$_2$ at 0.2 $\mu$g/kg/min decreased GMBF by 18.8±5.5% (n=5). Two $\mu$g/kg/min of PGE$_2$ significantly decreased GMBF by 46.2±11.2% (n=5) (Fig. 3). After PGE$_2$ administration was stopped, the decreased GMBF gradually reverted to basal levels. $l$-Isoproterenol (1 $\mu$g/kg/min) produced a significant 89.3±13.1% (n=5) increase in GMBF. PGE$_2$ infusion resulted in a significant fall in BP. HR increased immediately after PGE$_2$ infusion began and then decreased gradually. $l$-Isoproterenol caused a significant fall in BP and an increase in HR.

2. PGF$_2\alpha$: Intravenous infusion of PGF$_2\alpha$ at 2 $\mu$g/kg/min produced a biphasic response in GMBF, a significant increase of 30.6±4.2% (n=5) followed by a gradual decrease that led to a significant reduction of 20.5±4.4% in GMBF 45 min after the infusion was begun.
The GMBF had not recovered 1 hr after the PGF$_2\alpha$ infusion was stopped. Infusion of papaverine at 0.1 mg/kg/min caused no significant change in GMBF. BP and HR were not significantly affected by PGF$_2\alpha$.

Effects of i.v. infused PGE$_2$ on aspirin-induced gastric mucosal damage and on GMBF

This experiment was done to elucidate whether i.v. infused PGE$_2$, which decreases GMBF, prevents lesions induced by acidified aspirin. In period I, there were no significant differences between the control and PGE$_2$ groups in values of transmucosal PD, H$^+$ flux, Na$^+$ flux, and GMBF (Table 1). In period II, infusion of PGE$_2$ at the dose of 1 $\mu$g/kg/min, at which marked reduction of blood pressure was not observed, led to a significant increase in Na$^+$ flux and a slight decrease in GMBF, but PD and H$^+$ flux were not significantly affected. In period III in the control group, instillation of aspirin into the stomach induced a decrease in PD, increases in H$^+$ loss and Na$^+$ gain, and an increase in GMBF. Intravenous infusion of PGE$_2$ obviously diminished the changes in PD, H$^+$ loss,

| Periods | Intravenous infusion | Intragastric instillation | Potential difference (mV) | H$^+$ loss (µEq/30 min) | Na$^+$ gain (µEq/30 min) | GMBF (% of basal) | Lesion index (mm$^2$) |
|---------|----------------------|---------------------------|---------------------------|-------------------------|-------------------------|-------------------|-------------------|
| Control group (n=6) |                  |                           |                           |                         |                         |                   |                   |
| I       | Saline               | HCl                       | 40.3±1.8                  | 397±76                  | 265±44                  | 100               |                   |
| II      | Saline               | HCl                       | 39.7±1.6                  | 397±93                  | 243±54                  | 98.3±2.2         |                   |
| III     | Saline               | Asp+HCl                   | 20.0±3.4                  | 1595±149                | 1332±183                | 137.0±28.5       |                   |
| IV      | Saline               | HCl                       | 19.2±3.8                  | 1888±474                | 1720±372                | 151.0±19.2       | 743±101          |
| PGE$_2$ group (n=6) |                  |                           |                           |                         |                         |                   |                   |
| I       | Saline               | HCl                       | 41.4±1.6                  | 263±144                 | 362±73                  | 100               |                   |
| II      | PGE$_2$              | HCl                       | 40.4±1.9                  | 354±41                  | 777±120**               | 91.4±3.0         |                   |
| III     | PGE$_2$              | Asp+HCl                   | 31.0±3.2*                 | 681±171**               | 1005±82                 | 82.0±7.9         |                   |
| IV      | PGE$_2$              | HCl                       | 32.0±3.4*                 | 655±82*                 | 1186±52                 | 79.8±10.7**      | 17±8***          |

*1 At periods I, II and IV, the stomach was filled with the test solution (100 mM HCl, 15 mM NaCl, 78 mM mannitol and 40 mg/l phenol red). At period III, aspirin (5 mg/ml) suspended in the test solution was instilled into the stomach. *2 Prostaglandin E$_2$ (1 $\mu$g/kg/min) was infused i.v. during periods II, III and IV. *P<0.05, **P<0.01, ***P<0.001 as compared to the control group.
Na⁺ gain, and GMBF caused by aspirin. Aspirin-induced gastric lesions were markedly inhibited by i.v. infusion of PGE₂ from 743±101 mm² in the control group to 17±8 mm².

Discussion

The present study showed that the effects of PGE₂ and PGF₂α on GMBF varied with the routes of administration. Infusion of PGE₂ into the celiac artery increased GMBF, whereas infusion into the femoral vein decreased it. PGF₂α given i.a. caused a gradual decrease in GMBF, whereas given i.v., it produced a biphasic response: an increase in GMBF followed by a decrease. In contrast, l-isoproterenol given by either route of administration increased GMBF. Papaverine, a non-specific spasmolytic agent that has been reported to dilate gastric submucosal arterioles of the anesthetized cat (12), produced no significant increase in GMBF at the dose used in this study.

The reported results of the effect of PGE₂ on GMBF are not consistent. In the resting stomach, i.v. infusion of PGE₂ increased aminopyrine clearance in the rat (5), but not in the dog (6). Gerkens et al. (2) reported that bolus injection of PGE₂, 0.5 μg/kg, into the femoral vein produced a transient increase in left gastric arterial flow, as measured by an electromagnetic flow probe, in the anesthetized dog. On the other hand, i.a. infusion of PGE₂ reduced the gastric peripheral resistance and the gastric arterial perfusion pressure while inhibiting acid secretion in the histamine-stimulated canine stomach (7). PGE₂ infused into the splenic artery increased gastric arterial blood flow, as measured by an electromagnetic flow probe, while inhibiting pentagastrin-stimulated acid output in anesthetized dogs (8). Luminal instillation of 16, 16-dimethyl PGE₂ induced an increase in gastric venous flow in the resting stomach of the anesthetized dog (13).

Increased GMBF by i.a. infusion of PGE₂, as observed in this study, indicated that PGE₂ itself is a vasodilator in the gastric mucosal vessels. However, i.v. infusion of PGE₂ resulted in a decrease in GMBF. The vasodilating activity of PGE₂ may not be exerted when infused i.v. because 90–100% of PGE₂ is metabolized during one circulation through the lung or liver (14). The reduction in GMBF may be considered to be a secondary response due to the fall of systemic BP, the slight decrease of HR, and, in part, the suppression of acid secretion.

Gerber and Nies (15) suggested that discrepancies in the effect of PGs on GMBF arose from the use of the aminopyrine clearance technique. They observed that infusion of PGE₂ or PGI₂ into the splenogastric artery resulted in a significant gastric vasodilation as measured by the electromagnetic flow probe or the radiolabeled microsphere method. We obtained similar results by means of the aminopyrine clearance technique, suggesting that the inconsistent results reported so far are due not to the differences in the method of measurement but to differences in the route of administration. Other factors such as speed of injection and acid secretory state may also influence the effect of PGs on GMBF.

While PGF₂α is known as a vasoconstrictor in the peripheral vascular beds (16, 17), its action on GMBF has not been established. In the present study, i.a. infusion of PGF₂α caused a gradual decrease in GMBF, indicating that PGF₂α is a gastric mucosal vasoconstrictor. In contrast, i.v. infusion of PGF₂α produced a transient increase followed by a consistent decrease in GMBF. The initial change in GMBF by PGF₂α may be related to an increased HR and the constriction of systemic peripheral vessels. From the findings of i.a. infusion, we have concluded that PGE₂ and PGF₂α exert, respectively, a dilating and a constricting
activity on the gastric mucosal vessels. As relatively large amount of PGE$_2$ and PGF$_{2\alpha}$ are generated in the gastric mucosa (18), both PGs in this tissue probably play an important role in regulating GMBF, at least in dogs.

The findings of Robert (1) that PGs have cytoprotective activities on the gastrointestinal mucosa have been confirmed by a number of investigators. Several investigators have suggested that PGE$_2$ may mediate gastric cytoprotection through increasing GMBF (2, 3). Actually, the increase in GMBF prevented the mucosal injury induced by barrier breakers such as aspirin, alcohol, and bile salt (19, 20). Increased blood flow may help to dispose of H$^+$ ion either by buffering, dilution, or other processes that allow the surface cells to withstand exposure to increased penetration by the ion. On the other hand, several investigators suggested that changes in mucosal blood flow are not involved in cytoprotection by PGs. Puurunen (21) observed in the rat that PGE$_2$ protected the gastric mucosa against lesions produced by irrigation of the stomach with 30% ethanol in 0.1 N HCl without affecting GMBF. Barzilai et al. (22) observed the cytoprotective action of 16,16-dimethyl PGE$_2$ on sacs of isolated amphibian gastric mucosa, indicating that this action is independent of changes in mucosal blood flow. In the present study, the effect of PGE$_2$ on GMBF was altered depending on the route of administration. PGE$_2$ infused i.a. caused an increase in GMBF, suggesting that this increase may be involved in its cytoprotective mechanism. However, PGE$_2$ infused i.v. reduced GMBF, yet markedly inhibited lesion formation and breaking of the mucosal barrier caused by aspirin. Robert et al. (23) reported that PGE$_2$ showed cytoprotection of the gastric mucosa at a dose of 1% or less of its 50% antisecretory dose, which is probably the vasoactive dose. From these findings, PGE$_2$ seems to exert its cytoprotection mainly through mechanisms other than increasing GMBF. PGF$_{2\alpha}$, which is cytoprotective, is also likely to have a cytoprotective action through mechanisms other than increasing GMBF because PGF$_{2\alpha}$ markedly decreased GMBF by i.a. infusion in the present study. These results suggest that an increase in GMBF is not a common mechanism for the cytoprotective action of PGs.

Ritchie and Shearburn (24) reported that luminal instillation of taurocholate in acid solution elevated GMBF in the canine fundic mucosa, as measured by aminopyrine clearance. Cheung et al. (25) also found that during exposure of the canine gastric mucosa to alcohol, aspirin and bile salts, an increase in H$^+$ back-diffusion was accompanied by an increase in GMBF. The processes underlying the elevation of GMBF by topical barrier breakers are speculated to be a response of the mucosal microvasculature to the increased H$^+$ back-diffusion or to the release of local mediators (18). In the present study, topical application of aspirin resulted in increases of both GMBF and H$^+$ back-diffusion. PGE$_2$ given i.v. reduced the basal GMBF and prevented the aspirin-induced increase in GMBF. The abolishment by PGE$_2$ of the aspirin-induced increase in GMBF appears to be associated with the inhibition of H$^+$ back-diffusion.

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