Effect of Prostaglandin $F_{2\alpha}$ and Gastrin Pentapeptide on the Lower Esophageal Sphincter[1] (36825)

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The competence of the lower esophageal sphincter (LES) as measured by the height of its pressure recorded during intraluminal manometry appears to be the main factor in determining the occurrence of gastroesophageal reflux and esophagitis (1, 2). Recently, the gastrointestinal hormone, gastrin, has been shown to raise the LES pressure (3, 4). This investigation reports the effect of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in increasing the LES pressure in the intact opossum and compares its response with that of gastrin pentapeptide.

Materials and Methods. The opossum (*Didelphis virginiana*) was selected for these experiments because of the anatomical and physiological resemblance of its lower esophagus to that of human beings (5). Studies were done on 15 animals of either sex weighing between 2 and 3.5 kg. After anesthetizing with intraperitoneal sodium pentobarbital (50 mg/kg) the animals were strapped supine to the animal board. The LES pressures were continuously monitored with a water-filled polyvinyl catheter. An assembly of 3 polyvinyl catheters (i.d. = 0.86 mm and 0.d. = 1.17 mm) glued together with tetrahydrofuran, and with side openings 1 cm apart was connected to three pressure transducers. The catheters were constantly perfused with bubble-free water at a rate of 4.6 ml/hr through a constant infusion pump. The catheter system was calibrated by testing the system by applying known pressures at the tips before experiment. The catheter assembly was introduced through the mouth so that all the openings lay in the stomach. The assembly was then gradually withdrawn so that the middle opening was in the lower esophageal sphincter and the proximal opening lay in the body of the esophagus and the distal one still in the stomach.

A fresh solution of prostaglandin $F_{2\alpha}$ was prepared for each experiment by diluting 20 μl of the stock solution in 10 ml of 0.15 *N* saline. The stock solution was prepared by adding 0.1 ml of 95% ethanol and 0.9 ml of a solution of sodium carbonate (0.2 mg/ml) for each milligram of $PGF_{2\alpha}$ powder. Varying doses of $PGF_{2\alpha}$ were administered via an intravenous cannula as a single bolus. Five to ten minutes were allowed after the effect of the previous dose had completely disappeared. The pentapeptide of gastrin was dissolved in normal saline and was similarly used in different doses. The molar ratio between $PGF_{2\alpha}$ and pentagastrin was 1:1.3416. To serve as control normal saline and 20 μl of 9.5% ethanol in 20 mg/10 ml sodium carbonate diluted in 100 ml of normal saline (vehicle for $PGF_{2\alpha}$) were injected.

Results. Injection of normal saline or the vehicle for $PGF_{2\alpha}$ caused no change in sphincter pressure. Prostaglandin $F_{2\alpha}$ showed no effect with a dose of 0.25 μg/kg. In the higher doses, three different types of effects were seen (Fig. 1). The rise in sphincter pressure was observed in 77%, a fall in 15% and biphasic effect in 8% of experiments. These three different types of responses were neither dose dependent nor limited to certain animals. Table I summarizes these responses in different animals. The doses were given in random fashion and the influence of successive increasing or decreasing doses on the type of responses was not noted. The coefficient of variation (CV) varied with the doses used. With $PGF_{2\alpha}$ in the dose of 1 μg/kg the CV was 22% in the same animal as well as between animals. The mean CV was larger

[1] Supported in part by a grant from the Kelsey-Leary Foundation, Houston, TX.

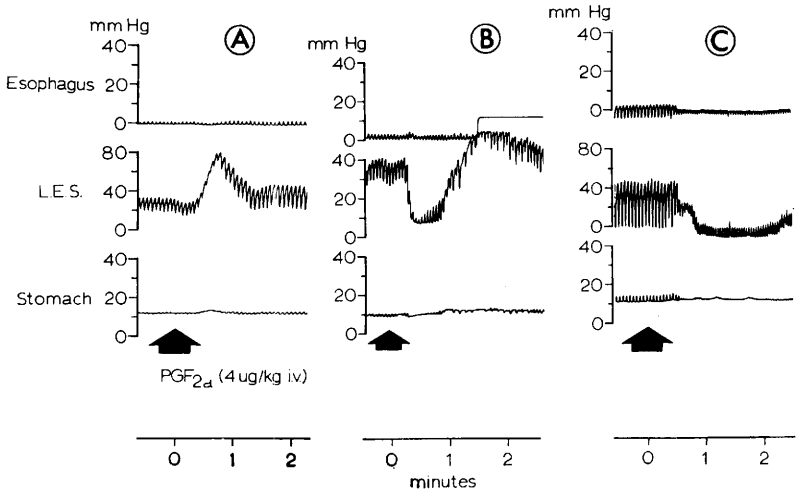

FIG. 1. Three different types of responses to iv injection of a bolus of PGF$_{2\alpha}$. The top lead recorded from the esophagus, the middle one from the lower esophageal sphincter (LES) and the bottom one from the fundus of the stomach. (A) shows rise in LES pressure which was seen in the majority of the experiments; (B) shows the biphasic response which occurred in 8% of the experiments; and (C) shows fall in pressure which occurred in 15% of the experiments.

with higher doses of 4 μg/kg being 27% in the same animal and 30.2% in different animals. The rising response of PGF$_{2\alpha}$ on LES as shown in Fig. 2 was dose dependent and peak action occurred at 4 μg/kg. The dose of 4 μg/kg caused more than 100% increase in sphincter pressure. The onset of action of PGF$_{2\alpha}$ occurred 20–180 sec (mean = 65 sec) after injection and lasted 0.25–19 min (mean = 5 min). The duration of action was not dose dependent.

TABLE I. The Number of Experiments Showing a Rise, a Fall or a Biphasic Response to Administration of PGF$_{2\alpha}$ in Different Animals.

Animal	No. of expts			
	Total	Showing rise	Showing fall	Showing biphasic
1	3	2	1	0
2	20	20	0	0
3	9	6	2	1
4	4	0	3	1
5	19	17	2	0
6	3	2	0	1
7	3	2	0	1
8	1	1	0	0
9	4	1	2	1
All animals	66	51	10	5

Gastrin pentapeptide also caused a dose dependent increase in LES pressure (Fig. 2). The maximum effect was observed with a dose of 2 μg/kg. The action of gastrin pentapeptide was seen 10–160 sec (mean = 44.5 sec) after injection and lasted 0.25–14 min (mean = 4.5 min). The duration of action was not dose dependent. The regression line using the doses of 0.5, 1, 2 and 4 μg/kg for the average increase in sphincter pressure vs log dose of gastrin pentapeptide was given by $y = 157 + 38.6\ x$ (coeff. corr. = 0.93) and of PGF$_{2\alpha}$ by $y = 48.5 + 40.8\ x$ (coeff. corr. = 0.96). However, because of the wide variation in individual values, particularly at higher dose levels, relative potency of the two agents could not be accurately determined.

Discussion. Bennett and Fleshler (6) recently reviewed the information on the effects of prostaglandins on the gastrointestinal tract. In general, PGF$_{2\alpha}$ causes contraction of circular as well as longitudinal muscle of the stomach, ileum and the large intestine *in vitro*, in experimental animals, and in man (7–9). In *in vivo* experiments, PGF$_{2\alpha}$ has been shown to cause increase in intestinal motility in the dog (10).

The present investigation reveals yet an-

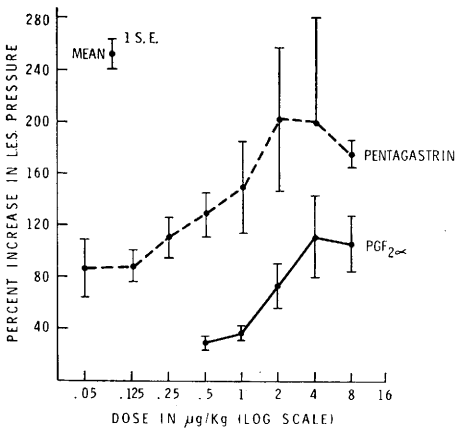

FIG. 2. Dose–response curves of the effect of PGF$_{2\alpha}$ (—) and gastrin pentapeptide (- -) on the increase in the lower esophageal sphincter pressure. Values for PGF$_{2\alpha}$ are calculated only from the 77%. of experiments that showed a rise in LES pressure. The number of observations constituting these experiments with PGF$_{2\alpha}$ in the doses of 0.5, 1, 2, 4 and 8 μg/kg were 13, 11, 8, 12 and 7, respectively. (These observations were obtained in 5, 4, 3, 4 and 3 animals, respectively.) The number of observations for pentagastrin were 6, 7, 9, 5, 7, 8, 4 and 3, respectively, for doses of 0.05, 0.125, 0.25, 0.5, 1, 2, 4 and 8 μg/kg. (These observations were obtained in 3, 4, 4, 3, 4, 5, 3 and 2 animals, respectively.)

other action of PGF$_{2\alpha}$, namely increasing the lower esophageal sphincter pressure in the opossum. The opossum esophagus, like that of man, is constituted of smooth muscle fibers in the lower 1/3 where they form both the circular and the longitudinal layers. Increase in the sphincter pressure was produced most frequently, occurring in over 3/4 of the experiments. In some experiments, however, this agent caused a fall in sphincter pressure or even a biphasic response. The reason for these responses is not clear. Such reponses were neither limited to certain animals nor were they dependent on the dose of PGF$_{2\alpha}$. It has been reported that the strips of tenia coli from human gut may respond with a contraction preceded by a small relaxation and at times only relaxation (9).

There is growing evidence for the involvement of prostaglandins in regulation of gastrointestinal motility in physiologic and pathologic states. Rashid has observed increased release of prostaglandins from the frog esophagus upon electrical stimulation (11). Such data in the opossum or human esophagus is not available, but would be of great interest in view of the very potent action of PGF$_{2\alpha}$ on the lower esophageal sphincter. Interestingly, PGE$_1$ and PGE$_2$ cause a reduction in lower sphincter pressure (unpublished data).

Pentapeptide of gastrin showed an increase in sphincter pressure. At all dose levels tested the gastrin pentapeptide causes greater increase in sphincter pressure. There is evidence to suggest that LES pressures are the main determinant in preventing gastroesophageal reflux and therefore agents which can improve sphincter competence may be of potential therapeutic value in patients with reflux esophagitis.

Summary. Prostaglandin F$_{2\alpha}$ was found to increase the lower esophageal sphincter pressure in the intact opossum *in vivo*. Dose response curves of the effect of PGF$_{2\alpha}$ showed that maximal response occurred with a dose of 4 μg/kg. The maximal response with gastrin pentapeptide occurred with a dose of 2 μg/kg for its action on increasing the lower sphincter pressure.

We thank Dr. John Pike of the Upjohn Company for a generous gift of prostaglandin and the Ayerst Company for gastrin pentapeptide.

1. Winans, C. S., and Harris, L. D., Gastroenterology **52**, 773 (1967).

2. Haddad, J. K., Gastroenterology **58**, 175 (1970).

3. Giles, G. R., Mason, M. C., Humphries, C., and Clark, C. G., Gut **10**, 730 (1969).

4. Cohen, S., and Lipshutz, W., J. Clin. Invest. **50**, 449 (1971).

5. Christensen, J. F., and Lund, G. F., J. Clin. Invest. **48**, 408 (1969).

6. Bennett, A., and Fleshler, B., Gastroenterology **59**, 790 (1970).

7. Fleshler, B., and Bennett, A., J. Lab. Clin. Med. **75**, 872 (1969).

8. Bennett, A., and Posner, J., Brit. J. Pharmacol. **42**, 584 (1971).

9. Bennett, A., Eley, K. G., and Scholes, G. B., Brit. J. Pharmacol. **34**, 630 (1968).

10. Shehadeh, A., Price, W. E., and Jacobson, E. D., Amer. J. Physiol. **216**, 336 (1969).

11. Rashid, S., J. Pharm. Pharmacol. **23**, 456 (1971).

Received Apr. 17, 1972. P.S.E.B.M., 1972, Vol. 141.