Abstract—Anaphylactic shock was induced with ovalbumin in sensitized rats and the relationship between PGE2 and cyclic nucleotides in lung tissue and plasma histamine during anaphylactic shock was studied. PGE2 level and cyclic AMP/cyclic GMP ratio decreased with this ovalbumin-challenge, and the former reached a minimum value 40 sec after the challenge while the latter reached a minimum value 20 sec later. The plasma histamine level was elevated and reached a maximum value concomitant with the minimum value in the cyclic AMP/cyclic GMP ratio. Dibutyryl cyclic AMP elevated the PGE2 level significantly and inhibited the ovalbumin-induced elevation of plasma histamine, however, this effect was abolished by the administration of indomethacin. PGE2 infusion elevated the cyclic AMP level as well as the cyclic AMP/cyclic GMP ratio, in a time-dependent manner, and inhibited the ovalbumin-induced elevation of plasma histamine during 10 min infusion. There was a significant correlation between the cyclic AMP level and the cyclic AMP/cyclic GMP ratio, both elevated by PGE2 infusion. Thus, anaphylactic elevation of the plasma histamine level results from a decrease in the levels of PGE2 in lung tissue rather than a decrease in the cyclic AMP/cyclic GMP ratio, albeit these decreases being coincident during anaphylactic shock.

Acute anaphylactic shock is a systemic allergic reaction which occurs in an appropriately sensitized individual following re-exposure to the challenging antigen. When the antigen contacts mast cells coated with immunoglobulin, IgE, the mast cells are degranulated and large amounts of histamine and slow reacting substance of anaphylaxis (SRS-A) are released (1, 2). Histamine induces a contraction of smooth muscle and dilatation of capillary beds. The most detrimental effects of histamine action in anaphylaxis are the constriction of bronchioles and bronchi and peripheral vasodilation after which there is a rapid fall in blood pressure (3).

Histamine release is inhibited by theophylline (4-6) in rats (4, 5) and this effect is dependent on adenosine-3',5'-cyclic monophosphate (cyclic AMP) (5, 7) which is known to play a role in the functional regulation of many organs (8). In a previous study, changes in cyclic AMP levels during anaphylactic shock were found to be dependent on prostaglandin (PG) E2 levels in lung tissue (4), such being considered a target organ of systemic allergic reaction in guinea-pigs (9-11). We suggested that the onset of anaphylactic

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shock may possibly result from a decrease in PGE₂ levels rather than a decrease in cyclic AMP levels in lung tissue. Recently, we reported that during anaphylactic shock, histamine release was promoted by agents that lower concentrations of cyclic AMP or elevate levels of guanosine-3',5'-cyclic monophosphate (cyclic GMP) (12). The cellular expression of extracellular stimuli by a bimodal action of cyclic nucleotides has also been suggested (13).

Since PGE₂ and cyclic nucleotides were thus assumed to be involved in onset of anaphylactic shock, in the present study we investigated the relationship between cyclic AMP/cyclic GMP ratio and PGE₂ content in lung tissue, and attempted to determine whether the onset of anaphylactic shock was due to changes in the cyclic AMP/cyclic GMP ratio or to changes in levels of PGE₂.

MATERIALS AND METHODS

Male Wistar rats 4 weeks of age underwent one week of acclimatization after purchase, then 0.5 ml of a 2% ovalbumin-complete adjuvant emulsion per rat was then given i.m. into the hind-leg twice a week for 5 weeks. After the sensitization, the antibody titre of IgG was about 64-fold and that of IgE was 43-fold. All experiments were carried out in sensitized rats anesthetized with sodium pentobarbital (30 mg/kg, i.p.). Anaphylactic shock was induced by i.v. administration of 0.2 ml of 2% ovalbumin-physiologic saline per rat.

Cyclic nucleotides and PGE₂ were assayed in the inferior lobe of the dextral lung.

Determination of cyclic nucleotides

Experimental animals were decapitated, the whole lung was excised and immediately fixed by focussed microwave irradiation (600W, 2,450 MHz) for 5 sec (14). The blood was washed out by physiologic saline via the pulmonary artery and the physiologic saline was removed by blotting paper. Each sample was prepared into 100 mg wet weight.

Cyclic AMP: For extraction of cyclic AMP, 1.0 ml of 6% (W/V) trichloroacetic acid (TCA) was added to the samples, and the mixture was homogenized. After centrifugation at 3,000 × g for 20 min and removal of a protein fraction, 0.1 ml of 1N-HCl was added. Extraction with a 2-fold volume of ethyl ether was repeated five times to remove TCA, then the remaining supernatant was warmed to 80°C in a warm bath in a draft, to completely evaporate the remaining ether. The liquid phase was lyophilized and was redissolved in 2.0 ml of a 50 mM sodium acetate buffer (pH 4.0), and this sample was preserved at −20°C. The quantitative determination of cyclic AMP was carried out by the protein binding method of Gilman (15).

Cyclic GMP: Cyclic GMP was extracted from the homogenates and purified by ion-exchange chromatography (16, 17). The tissue homogenate, containing 6% (W/V) TCA, was centrifuged at 27,000 × g for 30 min 50 μl of 4N-HCl were added to 4.0 ml of the supernatant, and this solution was extracted three times with 5.0 ml of ethyl ether. Two ml of the water phase was lyophilized, redissolved in 1.0 ml of 50 mM sodium acetate buffer (pH 4.0), and applied to a Dowex AG1-X8 column (0.5 × 5 cm) equilibrated with distilled
water. The column was washed with 10.0 ml of water and 10.0 ml of 2N-formic acid before the cyclic GMP was eluted with 14.0 ml of 4N-formic acid. The column eluate was lyophilized and redissolved in 0.5 ml of 10 mM sodium acetate buffer (pH 4.0) for determination of cyclic GMP concentration. Cyclic GMP was assayed according to the method of Illiano et al. (18).

All determinations of cyclic nucleotides were performed in duplicate.

Determination of plasma histamine

Plasma histamine levels were measured by a modified method of Shore et al. (19). Blood taken from the pulmonary artery was immediately centrifuged at 10,000 r.p.m. at 4°C for 10 min and plasma was obtained; a 9-fold volume of 0.4N-HClO4 was added to the plasma obtained, and the mixture was centrifuged at 3,000 r.p.m. at 4°C for 15 min. A protein fraction was then removed and histamine was extracted with butanol from the supernatants. After the extraction, histamine was coupled with O-phthalaldehyde (OPT) at a highly alkaline pH, and the fluorescent assay was conducted. The OPT from commercial source (Sigma Chemical Co.) was purified (20, 21) for the assay. Histamine fluorophor was read in a spectrofluorometer (Hitachi, 204) at the following wavelengths: activation, 360 mº; fluorescence, 450 mº.

Determination of PGE2

For the determination of PGE2, 200 mg wet weight of lung tissue was weighed and immediately 10-fold volume of 10-3 M-indomethacin/L-95% ethanol was added. Homogenization in a water bath kept at 0°C using a cooling circulator (Komatsu-Yamato, CTR-120) followed. Precipitates were allowed to remain overnight at 4°C (22) and were then centrifuged at 3,000 × g for 15 min. Each precipitate was washed with absolute ethanol three times and the supernatants were combined and evaporated to near dryness. The residues were redissolved in ethanol-water (2 : 1, by volume) and washed three times with petroleum ether (boiling point: 40-60°C). After removal of the petroleum ether phase, the ethanol was removed with a concentrator (Taiyo, TX-8) before acidification to pH 3.0 with 1N-HCl. The aqueous phase was then extracted three times with equal volumes of ethyl ether. The organic phases were combined, evaporated to dryness, and redissolved in acetatemethanol (3 : 1, by volume). Total PGs were separated into PGE1, PGE2, F16, and F26 by the stepwise development method (23) applied to thin-layer chromatography (TLC) on 5% (W/V) silver nitrate-sprayed silicagel HR plate after first development to separate the PGsE and PGsF. Solvent used in this determination; first step was chloroform—ethyl acetate—ethyl alcohol—acetic acid (200 : 200 : 7.5 : 10, V/V), the second step being the same after the silver nitrate was sprayed.

The determination of PGE2 was performed by the radioimmunoassay of a double antibody method according to the method of Levine et al. (24). In our method, final recovery of PGE2 was usually about 96%.

Drugs and treatments: Dibutyryl cyclic AMP sodium (P-L Biochemicals Co.); cyclic AMP assay kit, cyclic GMP assay kit (Boehringer Mannheim Co.); prostaglandin radio-
immunoassay kit (Clinical Assay Inc.); indomethacin (Sumitomo Kagaku Co.). Prostaglandin E₂ was a gift from Japan Upjohn Co. Other reagents were of analytical grade from commercial sources.

Dibutylryl cyclic AMP and indomethacin were administered in a volume of 0.1 ml/100 g body weight. Dibutylryl cyclic AMP was given (5 mg/kg, i.v.) 10 min before ovalbumin challenge. Indomethacin was given (10 mg/kg, i.p.) 15 min before ovalbumin-challenge or dibutylryl cyclic AMP administration. PGE₂ was infused (0.5 µg/50 µl/kg/min) via the femoral vein.

RESULTS

Interrelation of cyclic AMP/cyclic GMP ratio, PGE₂ and histamine during anaphylactic shock: Ovalbumin-induced changes in the cyclic AMP/cyclic GMP ratio and PGE₂ level in lung tissue and plasma histamine level in sensitized rats are depicted in Fig. 1.

A statistically significant decrease (P<0.05) in cyclic AMP was observed 20 sec after ovalbumin-challenge, and the cyclic AMP level continued to decrease. The cyclic GMP

![Graph](image-url)
level began to increase after the ovalbumin-challenge and the increase was significant (P<0.05) 20 sec after the challenge. Rapid decreases in the cyclic AMP/cyclic GMP ratio and PGE₂ levels were seen after the ovalbumin-challenge, the former reaching a minimum value in 60 sec and the latter in 40 sec. Regarding the plasma histamine level, a statistically significant increase (P<0.01) was seen 20 sec after ovalbumin-challenge and the plasma histamine level reached the maximum value 60 sec after the challenge.

**Effect of PGE₂ on cyclic AMP/cyclic GMP ratio**: Effects of PGE₂ infusion from zero to 20 min on cyclic nucleotides level in lung tissue are depicted in Fig. 2.

Cyclic AMP levels were elevated in a time-dependent manner, and there was a significant elevation (P<0.01) after a 5 min infusion. The cyclic GMP level was decreased significantly (P<0.001) during the 15 min infusion. The cyclic AMP/cyclic GMP ratio was elevated in a time-dependent manner, and a significantly high value (P<0.01) was observed after a 5 min infusion. There was a significant correlation (r=0.912, P<0.01) between changes in levels of cyclic AMP and changes in the cyclic AMP/cyclic GMP ratio, as induced by PGE₂ infusion (Fig. 3).

**Correlation of changes in the plasma histamine level and PGE₂ level in lung tissue during anaphylactic shock**: Plasma histamine level and PGE₂ levels in lung tissue were determined in rats either when anaphylactic shock was induced with ovalbumin or when dibutyryl cyclic AMP (Db-c-AMP), indomethacin, indomethacin plus Db-c-AMP, and PGE₂ were given as a pretreatment before the ovalbumin-challenge. Results were summarized in Table 1.

Ovalbumin-challenge produced a significant elevation in the level of plasma histamine (P<0.001; Table 1A) and this elevation was inhibited by Db-c-AMP. Indomethacin did

![Fig. 2. Influence of PGE₂ infusion on cyclic AMP/cyclic GMP ratio in lung tissue from sensitized rats. Each point represents the mean±S.D. from 5 experiments. Significance of difference from zero-time value assessed by Student's t-test --p<0.01; ----p<0.001.](image)
FIG. 3. Relationship between PGE₂ infusion-induced variations in cyclic AMP level and cyclic AMP/cyclic GMP ratio in lung from sensitized rats: the non-treated group (○), PGE₂ infusion for 3 min (■), for 5 min (▲), for 10 min (●), for 15 min (□), for 20 min (■).

TABLE 1. Effects of treatment with dibutyryl cyclic AMP, indomethacin and PGE₂ on ovalbumin-induced histamine changes in plasma or PGE₂ changes in lung from sensitized rats

(A) Histamine

| Group and treatment | (n) | Histamine (µg/ml plasma) before ALB | 60 sec after ALB | P* |
|---------------------|-----|-------------------------------------|------------------|----|
| None                | (6) | 0.094 ± 0.004                      | 0.227 ± 0.018    | <0.001 |
| Db-c-AMP            | (6) | 0.096 ± 0.006                      | 0.097 ± 0.007    | NS |
| Indomethacin (IDM) | (6) | 0.098 ± 0.007                      | 0.273 ± 0.024    | <0.001 |
| 10 mg/kg, i.p.      |     |                                     |                  |    |
| IDM + Db-c-AMP      | (6) | 0.092 ± 0.008                      | 0.235 ± 0.017    | <0.001 |
| PGE₂ infusion**    | (6) | 0.093 ± 0.005                      | 0.092 ± 0.006    | NS |
| 0.5 µg/50 µl/kg/min |     |                                     |                  |    |

(B) Prostaglandin E₂

| Group and treatment | (n) | PGE₂ (ng/g lung wet wt.) before ALB | 60 sec after ALB | P* |
|---------------------|-----|-------------------------------------|------------------|----|
| None                | (6) | 14.26 ± 0.64                       | 4.31 ± 0.38      | <0.001 |
| Db-c-AMP            | (6) | 21.84 ± 0.48                       | 20.63 ± 0.37     | NS |
| IDM                 | (6) | 5.19 ± 0.29                        | 3.14 ± 0.37      | 0.001 |
| IDM - Db-c-AMP      | (6) | 6.26 ± 0.33                        | 3.45 ± 0.17      | 0.001 |

ALB=2% ovalbumin 0.2 ml/rat i.v. *P values indicate the significance between values in the treatment before ALB and treatment after ALB. **PGE₂ infusion was continued for 10 min until ALB. Results are the mean ± S.E. NS = not significant at level of p<0.05. a: p<0.001 (VS. line 1)
not influence the ovalbumin-induced elevation of histamine level but did abolish the effect of Db-c-AMP in inhibiting the elevation in plasma histamine. PGF₂α infusion inhibited the elevation in plasma histamine. The level of PGF₂α was decreased significantly by the ovalbumin-challenge (P<0.001; Table 1B). Db-c-AMP elevated PGF₂α level significantly (P<0.001) compared with that of the non-treated group, and inhibited the decrease of PGF₂α level, as induced by ovalbumin-challenge. Indomethacin decreased the PGF₂α levels significantly (P<0.001) compared with the non-treated group and had no influence on the decrease of PGF₂α level as induced by ovalbumin-challenge. The effects of Db-c-AMP were also abolished.

DISCUSSION

Previous studies (4) showed that theophylline significantly improves the survival rate of anaphylactic rats and that this improvement is correlated with elevation of PGF₂α levels in lung tissue. The findings of the present study suggest that an intracellular control mechanism involving cyclic AMP and cyclic GMP during anaphylactic shock depends on the levels of PGF₂α, and that PGF₂α regulates the anaphylactic histamine release. It appears that cyclic AMP and cyclic GMP exert opposite effects and this may represent an example of the “Yin-Yang” theory first proposed by Goldberg et al. (13). Haberland (25) previously showed that alteration of cell functions and consequent release of histamine is an important component in the pathogenesis of anaphylactic shock.

In the present study, ovalbumin-challenge elevated plasma histamine levels, and decreased cyclic AMP/cyclic GMP ratio and PGF₂α levels in lung tissue significantly. The histamine level reached a maximum and cyclic AMP/cyclic GMP ratio reached a minimum 60 sec after the challenge, only the PGF₂α level reached a minimum 20 sec earlier (Fig. 1).

With regard to the relationship between PGF₂α and cyclic nucleotides, the following four findings suggest that during anaphylactic shock, there is a decrease of PGF₂α levels in lung tissue which is coincident with a decrease in the cyclic AMP/cyclic GMP ratio: 1) during anaphylactic shock, a decrease in PGF₂α levels precedes a decrease in the cyclic AMP/cyclic GMP ratio (Fig. 1), 2) PGF₂α infusion elevates cyclic AMP levels and cyclic AMP/cyclic GMP ratio in lung tissue in a time-dependent fashion (Fig. 2), 3) Db-c-AMP elevates PGF₂α level in lung tissue significantly (Table 1B), 4) a significant correlation was observed between the elevation of cyclic AMP level and that of cyclic AMP/cyclic GMP ratio in lung tissue both induced by PGF₂α infusion (Fig. 3).

With regard to the relationship between PGF₂α and histamine, anaphylactic elevation of plasma histamine may result from a decrease of PGF₂α level in lung tissue as: 1) the effect of Db-c-AMP which is considered to increase intracellular cyclic AMP levels (8, 26, 27) to which in turn inhibits anaphylactic elevation of plasma histamine, was attributed to the action of Db-c-AMP on increase of PGF₂α level, because the effect was abolished in the concomitant administration with indomethacin (Table 1A, B), a potent inhibitor of PGs biosynthesis (28, 29), 2) anaphylactic elevation of plasma histamine was inhibited when the levels of PGF₂α were maintained at high rates before challenge (Table 1A, B), 3) anaphylactic
elevation of plasma histamine was inhibited by PGE₂ infusion (Table 1A). This is in agreement with findings of other workers in which PGs inhibited the immunologic release of histamine from the lung (30, 31). In addition, we found that anaphylactic shock could be prevented by maintaining PGE₂ levels in lung tissue at a value observed before onset of anaphylactic shock (4).

Therefore, it may be concluded that the onset of anaphylactic shock in rats is due to the elevation of plasma histamine levels which results from a decrease of PGE₂ level in lung tissue rather than to a decrease of cyclic AMP/cyclic GMP ratio, though these decreases are coincident during anaphylactic shock.

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