PROSTAGLANDINS AND THE LUNG

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Jiro Nakano and Robert B. McCloy, Jr.

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13. ABSTRACT

The prostaglandins exert multiple potent pharmacological actions on different organs and tissues including the respiratory system. Although it is rather premature to conclude the precise physiological and pathophysiological roles of prostaglandins at the present time, a large number of recent observations implicate a close relationship between prostaglandins and pathogenesis and clinical manifestations of pulmonary disease. With reasonable certainty, the pathophysiological roles of the prostaglandins in respiratory disease will be clarified, along with a better understanding of pulmonary disease mechanisms. Furthermore, one can anticipate the synthesis of more potent and specific prostaglandin antagonists which may prove valuable in the treatment of respiratory disease.

UNIVERSITY OF OKLAHOMA
HEALTH SCIENCES CENTER

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INTRODUCTION

In 1933-34, Goldblatt (51,52) in England and Von Euler (43-45) in Sweden independently found that human seminal plasma and sheep seminal vesicle contain a potent lipid substance which exerts both smooth muscle stimulant and depressor actions. Von Euler named this substance prostaglandin (PG) since it was erroneously thought that PG is abundantly present in the prostate gland. Thereafter, little definitive information on the biochemistry and pharmacology of PG was obtained until Bergstrom and his associates (22-24) isolated and synthesized different pure prostaglandins (PGs) in 1957 (Fig. 1).

For the past several years, especially for the past two or three years, great progress has been made on the elucidation of the precise pharmacodynamic and biochemical actions of PGs, as larger quantities of pure PGs became available for experimental and clinical studies. It has been found that PGs exert numerous pharmacological actions in the body, which are summarized in Table 1. The purpose of this communication is to review the important developments in research on the biochemistry, pharmacology, pathophysiology and therapeutics of PGs in the respiratory system. Because of the phenomenally rapid and extensive progress of PG research, it is almost impossible to cite all available information. The reader should refer to recent monographs and reviews on PGs (17,44,62,63,102,103,124,139) for further details.

A. BIOCHEMISTRY OF PROSTAGLANDINS

1. Chemical Structure

All PGs are 20 carbon hydroxy fatty acids, and derivatives of prostanoic acid (17). As shown in Fig. 1, PGs of the E type (PGE_1, PGE_2, PGE_3) contain the characteristic 11α-hydroxy and 9-keto groups on a five membered ring. The PGs of the F type ($PGF_{1\alpha}$, $PGF_{2\alpha}$ and $PGF_{3\alpha}$) are analogous to the E type, but the 9-keto groups is reduced to a hydroxy group. In the PGs of the A type (PGA_1 and PGA_2) and of the B type (PGE_1 and PGB_1) the 11α-hydroxyl group is absent and the five membered ring structure is modified to form a 10,11 double bond and on 8,12 double bond, respectively. All of the naturally occurring PGs contain the 13,14 trans-double bond and a 15-S-hydroxy group. PGE_1, $PGF_{1\alpha}$, PGA_1 and PGB_1 contain only this one double bond, while PGF_2, $PGF_{2\alpha}$, PGA_2 and PGB_2 have an additional 5,6 cis double bond. PGE_3 and $PGF_{3\alpha}$ have three double bonds, 13,14-trans, 6,5 cis and 17,18 cis double bonds. Two groups of PGF isomers, i.e., PGF_1 , $PGF_{2\alpha}$ and $PGF_{3\alpha}$ and $PGF_{1\beta}$, $PGF_{2\beta}$, and $PGF_{3\beta}$ are so designated according to the α- or β-orientation of a hydroxyl group at C9. It appears that both the PGB group and the PGF_β group do not occur naturally, but are produced artificially during extraction of alkali treatment (17).

2. Distribution

All PGs listed in Fig. 1 occur in human seminal plasma which contains the highest PG concentrations in the body (17). Some of the PGs are also found in various other tissues such as lung, kidney,

brain, spinal cord, pancreas, liver, thymus, iris, umbilical cord and placenta. PGs also occur in menstrual fluid, amniotic fluid, and renal, splenic and adrenal venous bloods. Contrary to the PGs in semen, (predominantly PGE_1) the majority of tissue PGs in various species of animals and in humans including the respiratory system are either PGE_2 or $PGF_{2\alpha}$ (6,19,20). PGE_2 and $PGF_{2\alpha}$ have also been detected in human lungs (16,76,77) and the distribution in human lung is similar to that in most animals with a preponderance of $PGF_{2\alpha}$. Human bronchial muscle contains lower concentrations of PGs with slightly higher amounts of PGE_2. The concentrations of PGs in the lung are markedly less than those in semen (250 µg/ml). However, these concentrations are considered to be biologically very high, since the threshold concentrations of PGs for biological activities are usually 1 ng/ml or less in different bioassay systems. Furthermore, the venous blood concentrations of PGs after nerve or mechanical stimulation may increase to 200-300 ng/ml by novel biosynthesis of PGs in the tissue. Recently, some investigators concluded that the PGs measured in tissue are really released PGs and not PGs stored like neurotransmitters.

3. Biosynthesis and release

In 1964, Bergstrom et al. (18) and van Dorp et al. (40) independently found that, in sheep vesicular glands, a polyunsaturated 20 carbon fatty acid (PUFA), dihomo-γ-linoleic acid is converted into PGE_1 and $PGF_{1\alpha}$ while another PUFA arachidonic acid is converted into PGE_2 and $PGF_{2\alpha}$ (Fig. 2). A similar synthesis of PGs can occur in many tissues including lungs, kidneys, heart, stomach, liver, intestine,

placenta, brain and iris (14,17,82,110,123,124,131). It apears that PGs are not stored in the tissues but the precursors (PUFA) are present as moieties of the phospholipids in the cell plasma membrane or its vicinity (82,125,131). With a given appropriate stimulus, the magnitude of the biosynthesis (consequently release) of PGs is determined mainly by the amounts of the precursors available in the tissues (17,123,125,131). Hence, the tissue concentrations of PGs are markedly diminished in animals with essential fatty acid (PG precursors) deficiency (39). As shown in Fig. 3 and in Table 3, numerous mechanical, neuronal and chemical (hormones and drugs) stimuli activate phospholipase A in the cell membranes, and thus cleave the PUFA (82). Since PG synthetase(s) is abundantly present in the tissues including lungs (17,131), the cleaved PUFA are readily converted into the respective PGs and rapidly released in or near the cells or into the circulation, and exert a variety of biological actions (17,103,117,118). Recent observations (28,62,103,125,137) suggest that the cyclic AMP system is closely linked with the pharmacological actions of PGs. It has been postulated that the PGs may be involved in a negative feedback mechanism at the sites where the released neurotransmitters, acetylcholine and norepinephrine, and the circulating hormones exert their actions (62,125).

4. Metabolism

Anggard and Samuelsson (9-13) first found that PGE_1, PGE_2 and PGE_3 are converted into the respective 15-keto-PGE compounds by the oxidation of the secondary alcohol group at C15 in swine lungs. On the other hand, PGE compounds are converted into the respective di-

hydro-PGE compounds and 15-keto-dihydro-PGE compounds by the reduction of $^{13}\Delta$double bond in guinea-pig lungs. Likewise, PGF_1 and PGF_2 undergo similar metabolic pathway in guinea-pig lungs (54). Recently, it was found that PGE_1 is very effectively metabolized not only in swine and guinea-pig lungs but also in rat and human lungs (122,129). The enzymes which catalyze the oxidation and reduction of PGs have been identified as NAD^+ -dependent 15-hydroxy-prostaglandin dehydrogenase (PGDH) and $^{13}\Delta$prostaglandin reductase, respectively (9). PGDH has been purified from swine lungs (15) and has been found to be specific for PGs (15,105). Since either 15-keto-dihydro-PGE_1 exerts very little biological action, the oxidation with PGDH is the initial and major pathway by which PGs in the body are inactivated (7,100,104,105,131) (Fig. 4). A number of workers (16,49,64,102,106) showed that the magnitude of the depressor effect by the intra-arterial injection of PGE_1 is significantly greater than that obtained by the intravenous (i.v.) injection of the same dose of PGE_1 in dogs and man. Using the cascade bioassay technique (47,93, 120,141,142), it was shown that PGE_1 is greatly inactivated by the rat and dog lungs when injected intravenously, whereas dog and rat plasma inactivates PGs very little (47,98,113,115). Furthermore, it was found that the lung metabolized PGE compounds more rapidly than PGA compounds (64,93) since PGA compounds are poorer substrates than PGE compounds for PGDH (105).

In addition to the initial and major inactivation of PGs by PGDH and $^{13}\Delta$prostaglandin reductase, PGs are further degraded by non-specific beta- and omega-oxidation mostly in the liver. Recently,

beta-oxidation was also found to occur in the rat lung although its biological significance remains uncertain (114). The major urinary metabolites of PGE_1 is 5,7-dihydroxy-11-keto-tetranor-prostanoic acid (53,54,113). These oxidations are similar to other fatty acid metabolism in the liver mitochondria and microsomes, and do not appear to be a major inactivation process.

B. PHARMACOLOGICAL ACTIONS OF PROSTAGLANDINS ON THE NON-RESPIRATORY SYSTEM

As shown in Table 1, exogenously administered PGs exert a variety of biological actions in many species of animals and in man (17,44, 63,101,103). In addition, it has been shown that PGs modulate sympathetic activity by altering catecholamine release from adrenergic nerve terminals (57,59,71,72). PGE_1 and PGE_2 block and $PGF_{2\alpha}$ enhance norepinephrine release, thereby inhibiting or potentiating chronotropic action in the heart (59,148) and vasoactivities in the spleen and limb blood vessels (57,71,72). Because of the direct and indirect multiple biological actions of the PGs, many investigators have been tempted to postulate a number of attractive hypotheses to ascribe PGs to many physiological and pathophysiological conditions in man.

C. PHARMACOLOGICAL ACTIONS OF PROSTAGLANDINS ON THE RESPIRATORY SYSTEM

1. Effects of prostaglandins on isolated respiratory smooth muscle

Animal smooth muscle: $PGF_{1\alpha}$ or $PGF_{2\alpha}$ causes a weak contraciton of isolated tracheal smooth muscle from cats, rats and guinea-pigs, but nearly no effect in feline bronchial muscle (8,87). In isolated cat, guinea-pig, ferret or dog tracheal muscle, PGE_1 or PGE_2 not only reduces the tone but relaxes contraction induced by acetylcholine,

dihydroergotamine, histamine or $BaCl_2$ (87,140). Prior addition of PGE_1 was found to reduce the contraction induced by subsequent acetylcholine administration. Both PGE_1 and PGE_2 were effective in relaxing cat and monkey tracheal muscle. Recently, in cat tracheal muscle both PGA_1 and PGE_1 were found to inhibit acetylcholine-induced contraction essentially in proportion to concentrations (64). Although PGA_1 was about 30 times less active than PGE_1 as an inhibitor of tracheal muscle contraction, the effects of PGA_1 last considerably longer than that of PGE_1.

Human smooth muscle: Both PGE_1 and PGE_2 relax isolated human bronchial muscle, PGE_1 being slightly more potent than PGE_2 (132,136). In contrast, $PGF_{2\alpha}$ causes a marked contraction after a latent period of one minute during which there is sometimes slight muscular relaxation. $PGF_{2\alpha}$-induced contraction can be inhibited by either PGE_1 or PGE_2 but not by atropine or mepyramine (138). Like $PGF_{2\alpha}$, SRS-A (slow-reacting lipid substance produced in anaphylaxis of the isolated lung) also contracts isolated human bronchial muscle (34,88-90). Repeated high doses of SRS-A or $PGF_{2\alpha}$ render bronchial muscle strips insensitive but those made insensitive to $PGF_{2\alpha}$ still respond to SRS-A and vice versa (34). Both PGE_1 and PGE_2 still relax muscle strips which have been rendered insensitive to $PGF_{2\alpha}$. These observations suggest that SRS-A and $PGF_{2\alpha}$ are different substances. Collier and Sweatman (34) also showed that $PGF_{2\alpha}$-induced contraction of human bronchial muscle can be reduced by non-steroidal anti-inflammatory drugs such as fenamates.

The bronchial smooth muscle-relaxing effect of PGE_1 is not abolished by prior treatment with propranolol or phenoxybenzamine (132). Both propranolol and sotalol completely abolish the relaxation of human bronchial muscle produced by isoproterenol (2) but have no effect either on the PGE_2-induced relaxation or on the $PGF_{2\alpha}$-induced contraction. These observations indicate that the action of the PGs is not mediated through stimulation of adrenergic receptors.

2. Effects of prostaglandin on pulmonary airways resistance.

Animal studies: As shown in Fig. 5, in cats $PGF_{2\alpha}$ (15-30 µg/kg, i.v.) increases bronchial resistance (as measured by the Konzett-Rossler method) and right ventricular pressure whereas systemic arterial pressure and heart rate decrease markedly (8). Atropine abolishes the bradycardia but has no effect on the other cardiovascular changes or on the increase in pulmonary airways resistance. Since $PGF_{2\alpha}$ has little effect on isolated tracheal or bronchial muscle of the cat, it has been concluded that the increase in airways resistance is secondary to its effect on pulmonary vasculatures.

Although both PGE_1 and PGE_2 relax isolated tracheal muscle of the cat, Main (87) found that PGE_1 (0.3 µg/kg, i.v.) increases pulmonary airways resistance in the cat. In contrast, in rabbits and guinea-pigs, the PGE_1 antagonizes the increase in airways resistance induced by histamine or vagal stimulation and sometimes reduces the resting bronchial tone. Rosenthale et al. (126) found that PGE_1 (0.05-1 µg/kg, i.v.) or PGE_2 (4-8 µg/kg, i.v.) completely prevents bronchoconstriction caused by histamine, 5-hydroxy-tryptamine,

acetylcholine, bradykinin and SRS-A in anesthetized guinea-pigs (84,126). It has also been demonstrated that PGE_2 aerosol is effective in preventing histamine (aerosol)-and horse serum (aerosol)-induced bronchoconstriction in the conscious guinea-pig (84,126,127). Large et al. (84) showed that, against histamine-induced bronchoconstriction, the potency of the bronchodilator effects of isoproterenol and PGE_1 aerosol is similar although PGE_1 is slightly less active than isoproterenol and its duration is shorter (Fig. 6). In the guinea-pig by the i.v. route, PGE_1 exerts slightly more bronchodilator activity than PGE_2 while $PGF_{1\alpha}$ and $PGF_{2\alpha}$ are very weak bronchodilators (134). By the i.v. route both isoproterenol (0.2 µg) and PGE_1 (1 µg) increase the heart rate by a similar degree. An aerosol administration of PGE_1 (100 µg/ml) for 10 minutes causes no tachycardia while an aerosol of isoproterenol (1 µg/ml) given over the same period produces a marked tachycardia. Propranolol inhibits the bronchodilator effect produced by isoproterenol (aerosol) but not by PGE_1 or PGE_2 (aerosol) (2,127). Although PGE_1 is a more potent bronchodilator than isoproterenol, it appears to have less effect on the heart. There is considerable species variation in the bronchodilator effects of PG aerosols. In dogs, isoproterenol is completely effective in preventing the bronchoconstrictor effect (increased pulmonary resistance and fall in compliance) of histamine but the activity of PGE_2 is weak (127). In contrast, in the monkey, both isoproterenol and PGE_2 are effective and approximately equipotent bronchodilators. In the anesthetized cat, both PGE_1 and PGE_2 (aerosol) effectively reverse the bronchoconstriction induced by histamine,

5-hydroxytryptamine, bradykinin, methacholine or neostigmine (128) (Fig. 7 and 8). The bronchodilator effect of PGE_1 and PGE_2 (aerosol) is not associated with any significant cardiovascular effects whereas that of isoproterenol and aerosol is always accompanied by marked positive chronotropic and inotropic actions in cats (128) and dogs (128,147) (Fig. 9). Maximal bronchodilatation usually occurs within 2-3 minutes and lasts for 10-30 minutes. The duration of the bronchodilatation induced by PGE_1 and PGE_2 appears to be slightly less prolonged than or the same as that by isoproterenol (35,36,128). It has been concluded that in the cat or guinea pig both PGE_1 and PGE_2 are approximately 10-100 times more potent than isoproterenol as bronchodilators by aerosol administration (35,36,128).

Human studies:

a. Aerosol administration: In healthy subjects the bronchodilator effect of PGE_1 or isoproterenol aerosols is insignificant, probably because the bronchial smooth muscle of the airways is almost fully relaxed in these subjects (34). Inhalation of an aerosol of the triethanolamine salt of PGE_1 (PGE_1-TEA) has no effect on the forced expiratory volume in one second (FEV_1) and is better tolerated than the free acid. The effect of PGE_2-TEA by aerosol is indistinguishable from that of PGE_1-TEA in healthy subjects (38). PGE_1-TEA (55 µg) and placebo were administered to five asthmatic patients in a randomized manner (34). As seen in Fig. 10, the inhalation of either PGE_1 or isoproterenol increases the FEV_1 by a similar extent and duration, without producing any significant changes in the heart rate, blood pressure or ECG. With isoproterenol, the maximum broncho-

dilator effect is usually obtained immediately after the inhalation, then decreases slowly over the subsequent 60-90 minutes. The effect of PGE_1 appears less rapidly and the time of maximum bronchodilatation occurs approximately 30 minutes after the inhalation. Although bronchodilatation appears to be more persistent after PGE_1 than after isoproterenol, the overall duration of the effects of the two drugs is very similar. Most of the asthmatic patients experience retrosternal discomfort as the bronchodilator effect occurs after inhalation of PGE_1. As shown in Fig. 11, there is a slow but progressive fall in the FEV_1. Wheezing and bronchospasm occur when the FEV_1 has fallen to 2.3 liters but can be rapidly reversed by aerosol isoproterenol. A certain subject appears to be particularly sensitive to the irritant effect of inhaled substances since a modest fall in FEV_1 occurs after inhalation of the placebo. In this subject the time course of the progressive fall of FEV_1 associated with coughing suggests that the bronchospasm is reflex in origin and secondary to the irritant effect. The bronchodilator effects of PGE_2 aerosol in two asthmatic patients are similar to those of PGE_1. PGE_2 (5.5 - 55 µg) produces a 18 - 40% increase in the FEV_1 for 40-60 minutes duration. Hence, as a bronchodilator, PGE_2 is as effective as PGE_1 (38).

Herxheimer and Roetscher (60) also studied the effect of PGE_1-TEA aerosol (100 µg) in 37 patients with chronic obstructive pulmonary disease, using the non-forced inspiratory vital capacity and the maximum expiratory flow rate (peak flow) as an index of changes in airways resistance. In the majority of patients, PGE_1 improves vital

capacity and peak flow which are maximal 30 - 40 min after the inhalation. Seven patients with irreversible airways obstruction were not benefited by PGE_1, isoproterenol or salbutamol. Seven other patients given isoproterenol initially showed an improvement in vital capacity and peak flow but the subsequent administration of PGE_1 only resulted in further improvement in one patient. In 18 of the remaining 23 patients, the inhalation of PGE_1 significantly increased the vital capacity and peak flow. In 7 of these patients the response was good (peak flows increased by 13 - 48%) and in 4 only moderate (peak flows increased by 6 - 12%) but no further improvements could be maintained with isoproterenol or salbutamol. In 3 patients there was a good improvement with PGE_1 but isoproterenol caused at least an additional 15% increase in peak flow. Four patients showed a good response to PGE_1 but not to isoproterenol or salbutamol. In the remaining 5 patients there was no significant improvement with PGE_1 but a good improvement with isoproterenol. In this series, 25 of the 37 patients (67%) who experienced coughing after the inhalation showed no bronchodilator response to PGE_1 but a subsequent improvement on isoproterenol. Very recently, Hedqvist et al. (58) showed that aerosol inhalation of $PGF_{2\alpha}$ increased airway resistance in healthy subjects. The effect was relatively short-lasting and complete recovery occurred within 10 minutes. They concluded that the potency of the bronchoconstrictor action of $PGF_{2\alpha}$ is considerably greater than that of histamine.

b. Intravenous administration: Recently PGE_2 and $PGF_{2\alpha}$ have been rather extensively used intravenously for the induction of labor and therapeutic abortion (75,78). Smith (133) studied the effect of the i.v. infusion of PGE_2 or $PGF_{2\alpha}$ on pulmonary airways resistance in 15 patients who were subjected to therapeutic abortion (Fig. 12,13). Four of the patients had a family history of asthma, eczema or bronchitis but none suffered from asthma

or had any other cardiopulmonary disease at the time of the study. A control group consisted of 11 women who were undergoing minor gynecological operations. In 3 out of 8 patients, $PGF_{2\alpha}$ (25-200 µg/min, i.v.) caused no change in airways resistance. In the other 5, there was a significant increase in airways resistance although the dose at which the resistance rose varied between individual patients. No symptoms or signs of bronchospasm could be noted in any patient in this group. In 7 patients PGE_2 (2.5 - 20 µg/min, i.v.) caused a small increase in airways resistance. In 5 patients, there was a significant, dose-related increase in airways resistance. As in the previous group, there was no evidence of dyspnea, cough or bronchospasm, and in all patients, the airways resistance returned to normal on discontinuing the infusion. These results indicate that the i.v. infusion of PGE_2 or $PGF_{2\alpha}$ increases airways resistance in healthy subjects, presumably due to an increase in bronchial smooth muscle tone although the pressure of some bronchial edema cannot be excluded. Although none of the subjects had any respiratory difficulty in view of the changes in airways resistance, PGE_2 or $PGF_{2\alpha}$ should not be infused in patients with pre-existing obstructive airways disease. An increase in bronchial smooth muscle tone due to i.v. infusion of $PGF_{2\alpha}$ is in agreement with previous observations with this PG. The results with the i.v. infusion of PGE_2 are not in accordance with those of the previous study, i.e., bronchodilator effect of PGE_2 given by i.v. or aerosol in most species.

In most studies of the effects of the aerosol administration of PGs on the airways resistance, PGE_1 and PGE_2 are found to be more potent bronchodilators than isoproterenol on a weight basis although there is considerable species difference. In human subjects, small doses of PGE_1 or PGE_2 given by aerosol are effective bronchodilators, but the i.v. injection of either PGE_2 or $PGF_{2\alpha}$ increased airways resistance (35,36). The difference in the

bronchodilator activity of PGE_1 and PGE_2 when given by i.v. and aerosol routes may be caused by their metabolic inactivation in the pulmonary parenchymal tissues. PGs are found to be stable in the blood in vitro (47,98,113,115) but their half-life in the circulation is extremely short because they are rapidly inactivated in one circulation through the lungs of guinea pigs (47,122), rats (115), dogs (15), and man (107), as well as through the liver (131) and kidneys (99). It seems possible that a considerable amount of infused PGs are inactivated in the pulmonary circulation before reaching bronchial smooth muscle sites. It is also theoretically possible that PGs would reach bronchiolar smooth muscle through the airway route (aerosol) quicker than through the pulmonary capillary (i.v.) route. PGE_1 or PGE_2 given by aerosol is inactivated in the lungs shortly after the initiation of its bronchodilator effect. This would account for their high bronchodilator potency, relatively short duration of action, and lack of cardiovascular effects (84,128) (Fig. 14). Changes in the potency of PGs by aerosol in different species might reflect differences in their rate of inactivation (PGDH activity) and responsiveness of bronchial smooth muscle to PGs.

D. PHARMACOLOGICAL ACTIONS OF PROSTAGLANDINS ON THE PULMONARY AND NASAL MUCOSAL CIRCULATIONS

A number of investigators (49,91,96,97,101-103,111,112,129) found that i.v. administration of PGE_1 or PGE_2 0.1 to 4 µg/kg increases pulmonary arterial pressure in anesthetized dogs. In contrast in the isolated rabbit lung preparation, PGE_1 dilates pulmonary vascular beds and reduces pulmonary vascular resistance in both control dogs and dogs pretreated with propranolol and phentolamine (56). Likewise, in the isolated guinea-pig lung PGE_2 decreases and $PGF_{2\alpha}$ increases pulmonary vascular resistance due to their direct vascular actions (116). Neither mepyramine, propranolol nor phentolamine

modifies the vasodilator effect of PGE_2 or the vasoconstrictor effect of $PGF_{2\alpha}$, indicating that the vasoactivities of the two PGs are not mediated by the adrenergic and histaminogenic mechanisms in the pulmonary vasculature. In anesthetized dogs, it was also found that the i.v. or i.a. (pulmonary artery) injection of PGE_1 (1 μg/kg) decreases pulmonary arterial perfusion pressure when either cardiac input or pulmonary arterial blood flow is kept constant by means of a Sigmamotor pump (106,108). Both PGE_1 and PGA_1 cause a biphasic change in systemic venous return, an initial marked increase being followed by slight decrease before return to control values (42,106). Nakano and Cole (106) therefore concluded that PGE_1 and PGA_1 increase pulmonary arterial pressure by increasing the systemic venous return and pulmonary arterial blood flow. Hyman (66,67) showed that the infusion of PGE_1 (0.8-1.3 μg/kg/min for 10 min) into the pulmonary lobar artery decreases mean pulmonary arterial pressure, lobar arterial perfusion pressure and small pulmonary lobar vein pressure as systemic arterial pressure decreases in dogs, while the left atrial pressure remains unchanged. In anesthetized dogs, Giles et al. (49) found that the i.v. infusion of PGE_1 (0.33-0.67 μg/kg/min) decreases not only pulmonary vein pressure but also pulmonary blood volume. In contrast, Said (129) and Anderson et al. (4) found that PGE_2 increases both pulmonary arterial and venous pressures without producing any significant change in the left atrial and pulmonary wedge pressures in dogs and calves.

The i.v. administration of $PGF_{2\alpha}$ decreases systemic arterial pressure but increases heart rate, right ventricular systolic pressure and pulmonary arterial systolic pressure in cats (8,80,81). In contrast, the i.v. administration of $PGF_{2\alpha}$ (8-10 μg/kg) markedly increases pulmonary arterial pressure and slightly increases systemic arterial pressure in dogs (41,66,101-103, 106,111) (Fig. 14) and in calves (4). The i.a. injection of $PGF_{2\alpha}$ increases

the pulmonary arterial pressure even when pulmonary arterial blood flow is kept constant, indicating the direct vasoconstrictor action of $PGF_{2\alpha}$ (21). $PGF_{2\alpha}$ also directly constricts pulmonary veins and/or venules, and increases pulmonary venous pressure in dogs (41,66,110,129). Therefore, it can be concluded that the increased pulmonary arterial pressure by $PGF_{2\alpha}$ is most likely due to the constriction of pulmonary arterioles and in part to that of pulmonary veins. Very recently, Nakano and McCloy (110) showed that continuous i.v. infusion of $PGF_{2\alpha}$ slightly increases pulmonary arterial pressure and venous pressure although pulmonary airway resistance increases markedly. This can be due to slowly developing tachyphlaxis in the pulmonary vasculatures in the dog. It was also found that meclofenamate potentiates the hypertensive action of $PGF_{2\alpha}$ by increasing the responsiveness of the pulmonary vessels to $PGF_{2\alpha}$. The underlying mechanism for this phenomenon remains uncertain.

The injection of PGE_1, PGE_2, $PGF_{1\alpha}$ or PGA_1 into a common carotid artery constricts the small vessels in the nasal mucosa, resulting in a decrease in the airway resistance in the nasal cavity in anesthetized dogs (68,136). The magnitude of this action is essentially related to the dose. PGE_1 and PGE_2 are potent vasoconstrictors of the nasal blood vessels, the threshold dose ranging from 1 to 50 ng. The potency of PGA_1 and $PGF_{1\alpha}$ is about 1/100 that of PGE_1 or PGE_2. The maximum effect produced by PGE_1 or PGE_2 is about equivalent to that produced by an equal dose of epinephrine. However, the duration of the action of PGs is approximately 7 times longer than that of epinephrine. Likewise, Anggard (5) observed that the topical application of PGE_1 (10-15 μg) increases nasal patency through nasal mucosal vasoconstriction in 4 out of 7 human subjects. On the other hand, Jackson (68) showed that

the topical application of PGE_1 (27-100 µg) constricts nasal blood vessels for 3-12 hours in 5 out of 15 human subjects. Seven subjects occasionally had a similar response whereas the remaining 3 had no response to PGE_1. It remains uncertain whether prostaglandins exist in the nasal mucosa or how prostaglandins constrict the blood vessels in this particular area. Presently, the potential usefulness of PGE_1 as a nasal decongestant in man appears to be limited since the effectiveness of its topical application is rather unpredictable.

E. MECHANISM OF THE PHARMACODYNAMIC ACTIONS OF PROSTAGLANDINS ON THE RESPIRATORY SYSTEM

From the previous observations, it is evident that $PGF_{2\alpha}$ causes contraction of the isolated tracheal and bronchial smooth muscle from various species of animals. In contrast, PGE_1 and PGE_2 not only inhibit the intrinsic tone but also antagonize contractions produced by acetylcholine, histamine, dihydroergotamine, and $BaCl_2$ *in vitro* (87). Both PGE_1 and PGE_2 given i.v. or by aerosol similarly antagonize bronchoconstriction caused by histamine, serotonin, acetylcholine, bradykinin and SRS-A in various animal species *in vivo* (2,84,87,126,127). These observations suggest that PGE_1 and PGE_2 directly relax bronchial smooth muscle rather than acting as an antagonist to any particular biological bronchoconstrictor substance. In the isolated bronchial smooth muscle, the bronchodilator effect of PGE_1 and PGE_2 cannot be abolished by alpha- or beta-adrenergic blocking agents such as phenoxybenzamine and propranolol (2,131). Likewise, *in vivo*, the bronchodilator effect of PGE_1 or PGE_2 given i.v. or by aerosol is not affected by propranolol, reserpine, atropine and hexamenthonium or by such procedures as vagotomy, pithing or adrenalectomy (2,8,84,126,127). The increase in bronchial resistance induced by $PGF_{2\alpha}$ in cats is influenced by neither vagotomy nor atropine (8,81). The bronchodilator effects of PGE_1 and PGE_2 are therefore direct and not

mediated by sympathoadrenal stimulation. Likewise, the bronchoconstrictor action of $PGF_{2\alpha}$ is not likely to result from cholinergic stimulation or histamine release. Similarly, the pulmonary vasodilator action of PGE_1 and PGE_2, and the pulmonary vasoconstrictor action of $PGF_{2\alpha}$ are neither blocked by cholinergic nor adrenergic blocking agents (103).

It has been shown that the cyclic AMP system is closely linked to the mechanism of action of hormones and PGs (28,62,103,125,137). Both PGE_1 and PGE_2 stimulate adenyl cyclase and increase intracellular cyclic AMP in different tissues except adipose tissue (17,103). Both epinephrine and isoproterenol activate adenyl cyclase, and theophylline inhibits phosphodiesterase thus synergistically increasing the intracellular concentration of cyclic AMP in the rat lung (79,137). Hence, it has been postulated that the bronchodilator effect of epinephrine, isoproterenol or theophylline could be mediated by an increase in the concentration of cyclic AMP in the bronchial smooth muscle. Unfortunately, the precise effect of the PGs on cyclic AMP in the bronchial smooth muscle remains uncertain, partially because the lung consists of heterogenous tissues. However, it is conceivable that changes in the tone of bronchial smooth muscle are directly related to intracellular cyclic AMP levels. Even though effects of PGs on the bronchial smooth muscle are mediated through the cyclic AMP system, these effects are direct and not induced by adrenergic and cholinergic mechanisms since these effects were not blocked by cholinergic or adrenergic blocking agents. Recently, Adolphson et al. (1) showed that dibutyryl cyclic AMP produces relaxation in isolated guinea-pig tracheal muscle and that this effect is potentiated by theophylline. If PGE_1 and PGE_2 cause an increase in cyclic AMP in bronchial smooth muscle cells, this may be the mechanism responsible for bronchodilator effect. If so, one has to ascertain whether the bronchoconstrictor effect of $PGA_{2\alpha}$ is

due to its inhibitory action on the concentration of cyclic AMP in the bronchial smooth muscle.

F. PATHOPHYSIOLOGICAL ROLES OF PROSTAGLANDINS IN THE RESPIRATORY SYSTEM

It remains uncertain whether the PGs are involved in physiological and pathological pulmonary functions. Although entirely presumptuous, from many experimental observations, it is tempting to speculate on their possible roles in different pulmonary diseases. It is evident that the PGs are capable of exerting potent biological actions in the lung and other tissues (103). As pointed out by Piper and Vane (120), different stimuli have been found to release PGs from isolated perfused lungs of the guinea pig. The feature common to all of these procedures is probably mechanical distortion or damage or chemical (pharmacological and hormonal) stimulation to the cell membranes, and the release of PGs may follow any disturbance of the cell plasma membrane. When stimulated chemically or mechanically, PG concentrations in venous blood from the lung, kidney or spleen appears to be considerably higher than the tissue concentrations (122), and the tissues release more PGs than can be extracted (50,125). It seems that the release of PGs and their actions occur with PG biosynthesis augmented by different stimuli. Because both a potent bronchoconstrictor, $PGF_{2\alpha}$, and a potent bronchodilator, PGE_2, can be readily synthesized, it has been speculated that the PGs are somehow responsible for the regulation of normal bronchial smooth muscle tone, either acting as "tissue hormones" or having a strictly localized effect on release. Unfortunately, no study has been made to show that PGs play a role to support a local regulatory function. Such a function would necessitate the differential synthesis of PGE_2 and $PGF_{2\alpha}$ from the common precursor, arachidonic acid in response to changes in bronchial smooth

muscle tone (83). However, some indirect observations are worth consideration Karim (76) failed to detect any PGs in dog lung. This could be responsible for the weak bronchodilator effect of PGE_2 in this species (127). Conversely, the lungs of the guinea pig contain greater concentrations of $PGF_{2\alpha}$ than PGE_2 and this species PGE_1 and PGE_2 are particularly effective bronchodilators (84). These findings may be fortuitous but suggest that the presence or absence of the endogenous PGs is realted to their ability to affect bronchial smooth muscle. This might conceivably operate through a species and individual difference in the effects of the PGs on cyclic AMP.

PGs may also be involved in the physiological pulmonary ventilation-perfusion relationships. Although entirely speculative, it is possible to visualize that such substances, which have powerful effects on bronchial and vascular smooth muscle, may produce proportional changes in ventilation and pulmonary blood flow. It can be speculated that pulmonary distention increases pulmonary arteriolar resistance as well as airway resistance, and vice versa with pulmonary atelectasis or decrease in airways resistance.

Pulmonary embolism and infarct: In acute experiments, it has been shown that embolization of pulmonary artery branches with air, blood clot and a variety of particles is accompanied by a marked bronchoconstriction (29) and the release of PGs (86,120). It appears that $PGF_{2\alpha}$ is predominantly released and responsible for bronchoconstriction in this situation. It is not certain, however, whether the mechanical distortion or ischemia in the lung tissue due to pulmonary embolism directs the biosynthetic pathway of PGE_2 to that of $PGF_{2\alpha}$. In experimental pulmonary embolism, serotonin also is found to be released from platelets (3,139). PGs released as a result of embolization or from platelets (135) seem to be important mediators although their exact role has yet to be determined. Recently, in our laboratory in

control dogs, acute embolization of the pulmonary arterioles with $BaSO_4$ increased pulmonary arterial pressure and airways resistance (29). However, in dogs pretreated with indomethacin, $BaSO_4$ pulmonary emboli increases pulmonary arterial pressure but causes no effect on airways resistance, suggesting that the bronchoconstriction was induced by novelly synthesized $PGF_{2\alpha}$ as a result of pulmonary embolization. The precise biochemical mechanism through which the synthesis and release of PG are increased in pulmonary embolism and/or infarct remains unknown. It appears that multiple possible factors may be involved here including (a) mechanical and chemical insults on the pulmonary vasculature and its vicinity (120), (b) platelet release phenomenon (17,67) and (c) pulmonary ischemia (92).

Bronchitis, pneumonia and lung abcess: No study has been made on the effects of these inflammatory conditions in the respiratory system or vice versa. However, in the cutaneous infectious and arthritic lesions, the PGs have been found to be released, thus causing inflammatory manifestations such as swelling, redness, increased vascular permeability, exudation and pain (55,74). Furthermore, it has been fairly well-established that various pyrogens can stimulate the thermoregulatory centers in the hypothalamus to produce fever in animals (31,46,94,95,142). In addition, PGs appear to induce leukotaxis and other associated cellular responses in the inflammatory lesions (73,74). The underlying mechanism responsible for the pathogenesis of the inflammatory changes is illustrated in Fig. 17. Weissman and his associates (145,146,419,150) showed that PGs prevent the release of lysosomal enzymes by stabilizing the lysosomal membranes. From these observations, it is tempting to speculate that the inflammatory manifestations in the respiratory system are also accompanied by alteration in the biosynthesis and release of PGs in patients with bronchitis, pneumonia and lung abcess.

Pulmonary neoplasm: Again no definitive data is available for the pathophysiological role of PGs in the pulmonary neoplasm. It has been shown that PGs are released from thyroid carcinoma and other neoplasms and would cause certain systemic effects such as diarrhea. It is possible that the neoplastic tissues in the lungs and bronchi would increase PG synthesis and may cause certain respiratory symptoms such as bronchospasm and bronchial congestion.

Anaphylaxis: It has been shown that phytoagglutinin and other antigenic substances can release PGs in platelets and leukocytes (63,120). In the isolated perfused lungs of the guinea pig, ovalbumin was found to release PGs (120,121). PGs are also released in anaphylactic reactions but it is again difficult to determine the magnitude of their contribution to the bronchoconstriction because other highly active substances such as histamine and SRS-A are released at the same time (32).

Bronchial asthma and bronchiectasis: The pathophysiological role of the PGs on the genesis of bronchospasm in bronchial asthma and bronchiectasis remains uncertain although Hedqvist et al. (58) have postulated that $PGF_{2\alpha}$ may participate in the pathogenesis of bronchial asthma in man. It has been clearly demonstrated, however, that alveolar overdistension results in an increased synthesis and release of PGs (26,120,130). This observation strongly suggests that bronchospasm is not only caused by the PGs but also results in further synthesis and release of the PGs. Obviously, if a novelly synthesized PG were $PGF_{2\alpha}$, it would result in a vicious cycle of bronchospasm. On the other hand, if it were PGE_2, bronchospasm would be relieved by its bronchodilating action. Presently, no information is available on the distribution of PGs in the lungs or bronchi of asthmatic patients. If PGs in the lungs are indeed involved

in the physiological and pathological regulation of bronchial smooth muscle tone, it may be speculated (62) that the overproduction of the bronchoconstrictor $PGF_{2\alpha}$ from arachidonic acid at the expense of the bronchodilator PGE_2 might contribute to the bronchospasm and the increase in sensitivity of respiratory smooth muscle which occurs in bronchial astham. Alternatively, PGE_1 and PGE_2 may be converted to, respectively, $PGF_{1\alpha}$ and $PGF_{2\alpha}$ in the lungs. However, Bergstrom et al. (17) and Samuelsson (131) showed that no interconversion between PGE_1 and $PGF_{1\alpha}$ or between PGE_2 and $PGF_{2\alpha}$ occurs in synthesis. Another possible mechanism is that the defect in bronchial asthma is not due to disturbances of the biosyntehsis and distribution of PGs but to those of the cyclic AMP system in the bronchial smooth muscle (137). A reduced intracellular concentration of cyclic AMP (a failure of activation of adenylcyclase or increased activity of phosphodiesterase) would probably result in an increase of the bronchial smooth muscle tone. The PGs might well be involved if they are shown to stimulate or inhibit adenylcyclase in the bronchial smooth muscle as in other tissues. Very recently, Smith and Parker (134) showed that considerable difference exists in the responsiveness of leukocyte cyclic AMP to isoproterenol, norepinephrine, PGE_1 and cortisol between healthy subjects and symptomatic asthmatic patients. The magnitude of the increase in leukocyte cyclic AMP induced by these agents was markedly greater in normal individuals than in asthmatic patients. This observation suggests that some fundamental biochemical abnormality could exist in the cyclic AMP system and/or PGs in asthmatic patients.

G. EFFECTS OF THE PROSTAGLANDIN BIOSYNTHESIS INHIBITORS OR RECEPTOR ANTAGNOISTS ON THE RESPIRATORY RESPONSE TO PROSTAGLANDINS

Aspirin-like drugs (prostaglandin biosynthesis inhibitors): Collier et al. (30-32) have studied the antagonistic action of non-steroidal anti-inflammatory drugs over biological substances believed to be involved in allergic reactions. An interaction was suggested to exist between these drugs and the PGs since the fenamates, phenylbutazone and aspirin were found to effectively antagonize the $PGF_{2\alpha}$-induced contraction of isolated human bronchial muscle (34). This antagonism appeared to be selective since there was no block of the relaxant effect of PGE_1 or PGE_2. A clue to an effect of the non-steroidal, anti-inflammatory drugs on PG synthesis was first provided when aspirin and sodium salicylate were found to antagonize the bronchoconstrictor effect of arachidonic acid, a PG precursor, in both isolated human bronchial muscle and in the guinea-pig in vivo (25,70). Recently it has been shown that indomethacin and aspirin are potent inhibitors of the syntehsis of both PGE_2 and $PGF_{2\alpha}$ in guinea-pig lung homogenates (121, 142, 143) (Fig. 15). Indomethacin and aspirin were effective in low concentrations (0.27 and 6.3 µg/ml) respectively, giving 50% inhibition of synthesis. These concentrations are within the range achieved in the plasma in therapeutic doses. The order of potency of aspirin and sodium salicylate in inhibiting PG synthesis is similar to their order of potency in antagonizing the bronchoconstrictor effect of bradykinin in the guinea-pig (33,34). This further suggests that bradykinin and other mediators released in anaphylaxis produce bronchospasm by stimulating the synthesis and release of $PGF_{2\alpha}$. Amidopyrine, phenazone, phenylbutazone, aspirin and indomethacin have all been reported to be of benefit to asthmatic patients (38,61,69,119)

although the response is variable and these drugs have never become established in treatment. In view of the recent findings of Vane (142) it seems possible that the beneficial effects of this group of drugs in asthma may be due to inhibition of the synthesis of $PGF_{2\alpha}$ and perhaps other related mediators.

The observation on the non-steroidal anti-inflammatory drugs as powerful inhibitors of PG synthesis provides a new approach to the study of these substances in the maintenance of bronchial smooth muscle tone. Since PGE_2 and $PGF_{2\alpha}$ have different and mutually antagonistic actions on bronchial smooth muscle, it is necessary to develop selective inhibitors before individual contributions can be determined. In spite of its marked inhibition of $PGF_{2\alpha}$-induced constriction of the tracheal smooth muscle in vitro (30,31), the i.v. injection of meclofenamate was found to be ineffective in blocking the increase airway resistance induced by $PGF_{2\alpha}$ in cats (81) and in dogs (110).

Prostaglandin Antagonists: Since PGs appear to play a role on the pathogenesis of different pulmonary diseases, it is important to develop compounds which block the pharmacodynamic effects of specific PGs (PGE_1 and $PGF_{2\alpha}$). As listed in Fig. 15, a number of compounds which block the effects of the PGs on various smooth muscle preparations have been recently synthesized (48,85,144) (Fig. 18). Polyphloretin phosphate (PPP), a polymeric phosphorylated polyanionic derivative of phlorizin, has been shown to block the $PGF_{2\alpha}$-induced contraction of the isolated human bronchial smooth muscle while leaving the relaxant effect of PGE_2 unaffected (85,88,90,144). However, i.v. injection of PPP had no effect on the PGE_2-induced bronchoconstriction in cats (82) nor on the $PGF_{2\alpha}$-induced pulmonary arterial hypertension in dogs (Nakano, unpublished data). Compounds presently available are either relatively non-specific or too toxic for administration to man. However, the development of specific and potent PG antagonists as therapeutic agents

or pharmacological agents is very important to a further understanding of the role of the PGs in the regulation of bronchial smooth muscle tone and to a treatment of patients with bronchospasm.

H. POSSIBLE THERAPEUTIC APPLICATIONS OF PROSTAGLANDINS

It remains uncertain whether the PGs will have any therapeutic application in respiratory disease but it is appropriate to appreciate the advantages and disadvantages of the PG preparations already studied in asthmatic patients and to possible future developments. PGE_1 and PGE_2 have been shown to be effective bronchodilators when given by aerosol to asthmatic patients and this activity is detectable with delivered doses as small as 2-5 µg. Animal and limited human data support the view that both PGE_1 and PGE_2 are considerably more active than isoproterenol on a weight basis by the aerosol route. PGE_1 and PGE_2 are rapidly metabolized in the lungs in experimental animals. If this also appears to occur in man (107) it may be the reason why doses of the PGs which cause substantial bronchodilatation do not appear to have any effect on the cardiovascular system. Inactivation of PGs in the lungs by PGDH may also account for the relatively short bronchodilator action which is comparable to that of isoproterenol.

Despite their several advantages it seems unlikely that any natural PG will prove to be a bronchodilator of therapeutic value. This is simply because all the aerosol preparations of PGE_1 and PGE_2 irritate the human upper respiratory tract (35-37,60). PGs are weak acids and an aerosol of the neutral TEA salt was better tolerated but was not entirely free from irritant effects. It is not yet clear whether this local effect on the upper respiratory tract is a characteristic feature of the PG molecule or is limited to the naturally-occurring PGE_1 and PGE_2. Another problem is that

PGE_1 and PGE_2 are not particularly stable in alcoholic solution as pressurized aerosols and slowly lose their activity over a period of several months.

In order to use PGs as therapeutic agents, it is necessary to synthesize more ideal PGs which have the following properties: a) potent specific bronchodilators; b) no effects on tissues other than those in the airways; c) free of bronchial irritant effects; d) resistant to metabolic inactivation in the g.i. tract, liver and lung. If such PG analogues can be prepared they will be extremely effective in the treatment of patients with bronchial asthma. Another approach is by modification of the formulation. All the PG aerosols so far tested have been found effective but it is likely that nanogram quantities are actually reaching the bronchiolar smooth muscle and producing relaxation. PG preparations in a micronized form may be able to improve their deposition in the airways which has been successfully employed in the formulation of isoproterenol and salbutamol aerosols. Although the relationship of the PGs to the relaxation of bronchial smooth muscle is obscure, it is conceivable that a hypothetical deficiency of PGs in bronchial asthma might be corrected by their prophylactic use.

CONCLUSION

The prostaglandins exert multiple potent pharmacological actions on different organs and tissues including the respiratory system. Although it is rather premature to conclude the precise physiological and pathophysiological roles of prostaglandins at the present time, a large number of recent observations implicate a close relationship between prostaglandins and pathogenesis and clinical manifestations as of pulmonary disease. With

reasonable certainty, the pathophysiological roles of the prostaglandins in respiratory disease will be clarified, along with a better understanding of pulmonary disease mechanisms. Furthermore, one can anticipate the synthesis of more potent and specific prostaglandin antagonists which may prove valuable in the treatment of respiratory disease.

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Table 1

PHARMACOLOGICAL ACTIONS OF PROSTAGLANDINS

1. Cardiovascular system

Positive inotropic and chronotropic actions
Increase pulmonary arterial pressure
Increase cardiac output. Increase capillary permeability
PGE and PGA: Decrease systemic arterial pressure and venous pressure. Increase the regional arterial blood flows. Increase coronary blood flow.
PGF: Increase systemic arterial pressure and venous pressure. Decrease regional arterial blood flows.

2. Gastrointestinal system

Decrease gastric acidity
Increase intestinal motility
Increase gastric motility
Induce vomiting and diarrhea

3. Respiratory system

PGE_1 and PGE_2: Bronchial dilation
PGF_2: Bronchial constriction - Asthma (SRS-C)

4. Hematological system

PGE_1: Inhibition of platelet aggregation and stimulation of adenyl cyclase. Increase the production of erythropoietin.
PGE_2: Stimulation of platelet aggregation.

5. Renal and urinary system

Increase renal blood flow, glomerular filtration and urinary flow.
Antagonize vasopressin action-water diuresis.
Increase urinary Na and K excretion.
Antagonize renin-angiotensin mechanism (?).
Increase ureter motility and bladder motility.

6. Reproductive system

Increase tubal motility. Increase uterine motility and tone in pregnancy.
Luteolysis in vivo. Contraceptive action (Luteolysin).
Induction of labor and abortion.
Increase sperm motility.

7. Endocrine system and Metabolism

Increase the adenyl cyclase activity, cyclic AMP levels and the secretion of the hormones in the pituitary and target glands in vitro.
Antagonize the hormone-stimulated lipolysis in adipose tissues.
Antagonize the hormone-stimulated glycogenolysis.

8. Central Nervous System

Induce stupor or catatonia and excitement in some species of animals.
Block sympathetic stimulation. Inhibit spinal reflex.
Pulsating headache.
Stimulation of the hypothalamic and medullary centers. Fever.

9. Eye and Nose

Miosis. Increase intraocular pressure.
Decrease the airway resistance in the nasal center (vasocontriction).

10. Skin and Joint

Hyperemia, erythema, exudation, swelling, pain and increased permeability.
Increase keratinization.

Table 2

CONCENTRATIONS OF PROSTAGLANDINS IN LUNGS OF DIFFERENT SPECIES OF ANIMALS

Origin	Concentrations (ug/g)		Remarks	References
Human lung	PGF_2	0.02	24 hr after death	Anggard 1964 & 1965
Monkey lung	PGF_2	0.2	3 hr after death	Anggard 1965
Pig lung	PGF_2	0.4	Fresh	Bergstrom et al. 1960
Sheep lung	PGF_2	0.5	Fresh	Bergstrom et al. 1962
	PGF_2	0.04	Fresh	Anggard
Bovine lung	PGF_2	0.3	Fresh	Anggard 1964
Guinea pig lung	PGF_2	0.5	Fresh	Anggard 1965

Table 3

PHYSIOLOGICAL AND PHARMACOLOGICAL RELEASE OF PROSTAGLANDINS FROM TISSUES

SITE (SPECIES)	STIMULI
NERVOUS SYSTEM	
Somatosensory cortex (cat)	Spontaneous release, sensory nerve or cortical stimulation, and analeptics
Cerebral ventricels (cat and dog)	Spontaneous release and serotonin
Hypothalamus (cat)	Vaccine, and nerve stimulation
Cerebellar cortex (cat)	Spontaneous release
Spinal cord (frog)	Spontaneous release, sensory nerve stimulation and analeptics
RESPIRATORY SYSTEM	
Lung (guinea pig and dog)	Phospholipase A, distention, massage, particles, air, embolism, anaphylaxis histamine, tryptamine, and serotonin
Diaphragm (rat)	Nerve stimulation and norepinephrine
GASTROINTESTINAL SYSTEM	
Stomach (rat)	Vagal stimulation, transmural stimulation, pentagastrin, histamine, Carbachol serotonin and stretch
Intestine (frog)	Spontaneous release, distention and phospholipase A
Spleen (dog and rabbit)	Nerve stimulation, epinephrine, colloid particles and distention
Liver (rat)	Glucagon
ENDOCRINE SYSTEM AND METABOLISM	
Adrenals (rat and rabbit)	Acetylcholine
Thyroid (man)	Spontaneous release
Adipose tissue (rat and rabbit)	Nerve stimulation, norepinephrine ACTH, growth hormone and glucagon
REPRODUCTIVE SYSTEM	
Uterus (guinea-pig and man)	Distention, mechanical stimulation, parturition and estrogen
RENAL SYSTEM	
Kidney (dog)	Ischemia, norepinephrine and angiotensi
Urinary bladder (rat)	Distention
OTHERS	
Eye (rabbit and man)	Mechanical stimulation and spontaneous release
Skin (rat, frog, and man)	Carrigeenin, isoproterenol, and spontaneous release
Platelet (man)	Thrombin

FIGURE LEGENDS

Fig. 1. Chemical structure of naturally occurring prostaglandins.

Fig. 2. Biosynthesis of prostaglandins.

Fig. 3. Diagram showing the possible mechanism for synthesis and release of prostaglandins.

Fig. 4. Metabolism of prostaglandins.

Fig. 5. Effects of intravenous injection of PGF_2 on the pulmonary airways resistance and circulation before and after atropine in the cat (Anggard and Bergstrom, 1962).

Fig. 6. Relative bronchodilator potencies of PGE_1 and isoproterenol (isoprenaline) in anesthetized guinea pigs when give either intravenously or by aerosol (Large et al., 1969).

Fig. 7. Effects of PGE_2 on heart rate, blood pressure, tidal volume, transpulmonary pressure and respiratory flow rate in the anesthetized cat infused with neostigmine for 6 min. The break of the record represents the temporary disconnection of the pneumotachograph during the time needed to administer drug. (Rosenthale et al., 1971).

Fig. 8. Percent reduction of cholinergic-induced pulmonary airway resistance changes in the cat by aerosol (Upper Figure) or i.v. (Lower Figure) administration of PGE_1, PGE_2 or isoproterenol. (Rosenthale et al., 1971).

Fig. 9. Effects of PGE_1, PGE_2 and isoproterenol on systolic and diastolic blood pressures (BP), systolic and diastolic left ventricular pressures (LVP), left ventricular dp/dt, right ventricular (RV) contractile force and heart rate (HR) in anesthetized dogs. (Wendt and Baum, 1971).

Fig. 10. Effect of aerosol inhalation of PGE_1-TEA (o) and isoproterenol (•) on the forced expiratory volume in one second (FEV_1) in 5 asthmatic patients. Shaded area represents mean changes in FEV_1 after administration of placebo (Cuthbert, 1969).

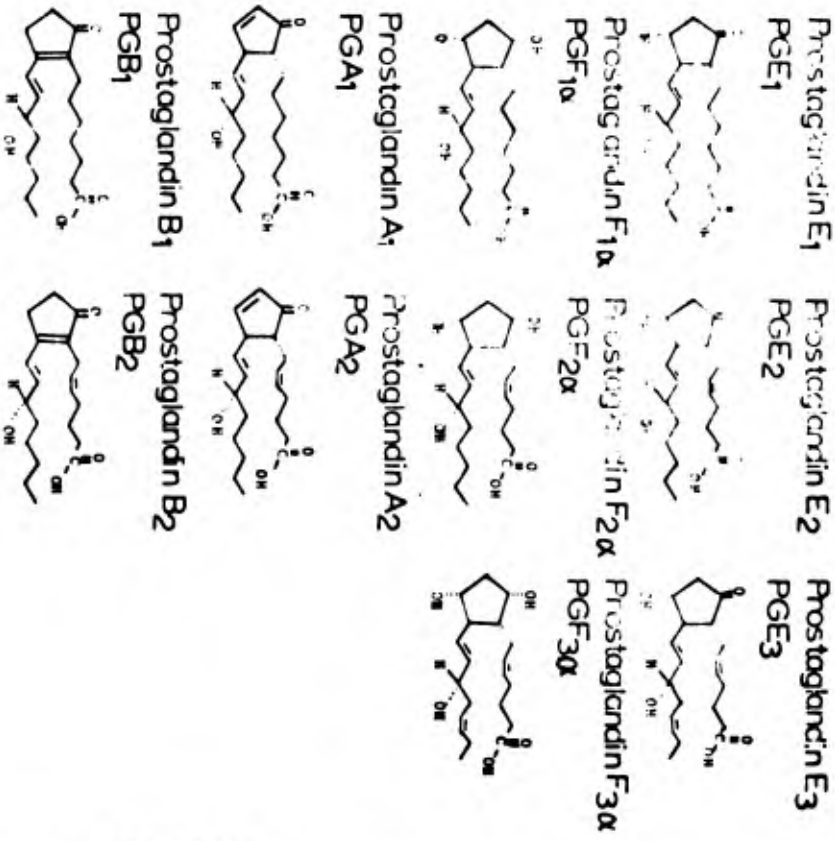
Fig. 11. Effect of i.v. administration of PGF_2 on the pulmonary airways resistance (R_t) in a healthy woman undergoing therapeutic abortion. (Smith, 1972).

Fig. 12. Effect of the i.v. administration of PGE_2 on the pulmonary airways resistance (R_t) in healthy women undergoing therapeutic abortion. (Smith, 1972).

Fig. 13. A comparison of the bronchodilator and circulatory effects of PGE_1 and isoproterenol given by aerosol and by i.v. injection.

Fig. 14. Effects of the i.v. administration of PGE_1 (Upper Tracing) and PGF_2 (Lower Tracing) on heart rate (HR), mean pulmonary arterial pressure (MPAP), mean left atrial pressure (MLAP), mean systolic arterial pressure (MSAP), cardiac output (CO) and myocardial contractile force (MCF) in anesthetized dogs. (Nakano, 1971).

Fig. 15. Chemical structure of the inhibitors of prostaglandin synthetase and prostaglandin receptor antagonists.



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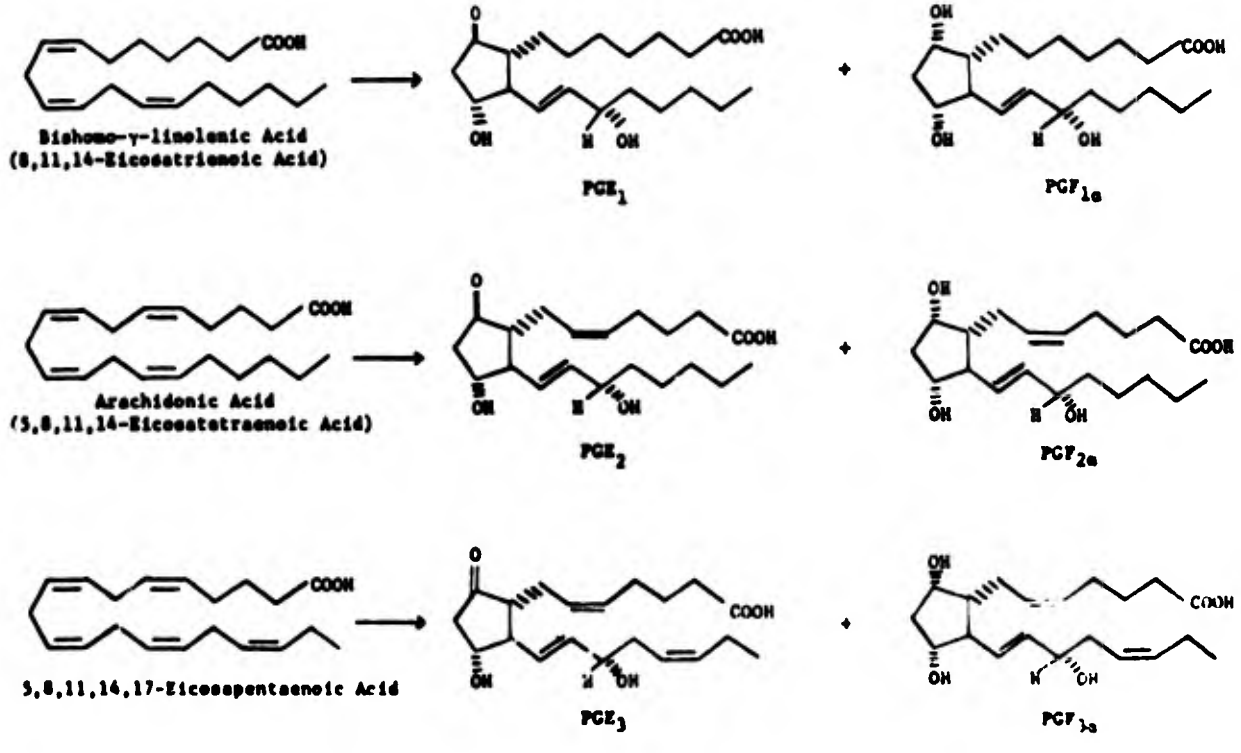
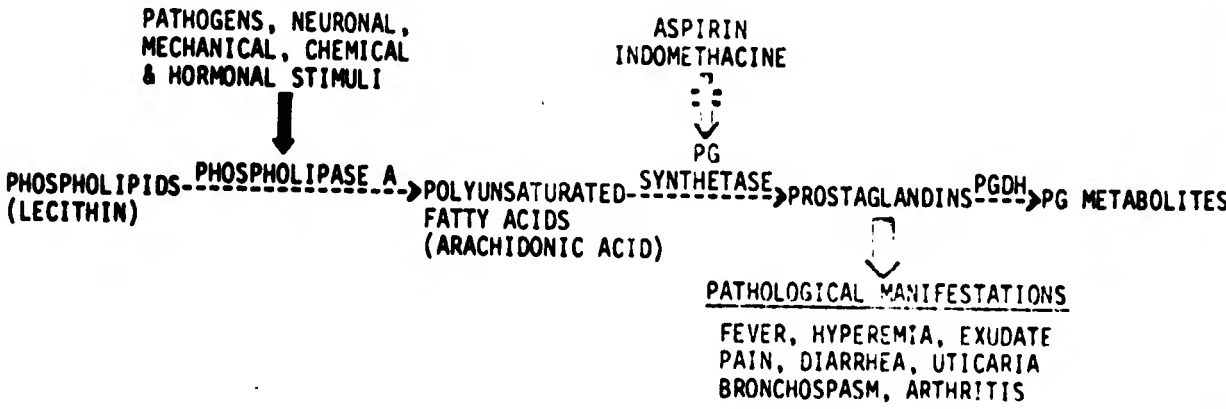


FIGURE 2



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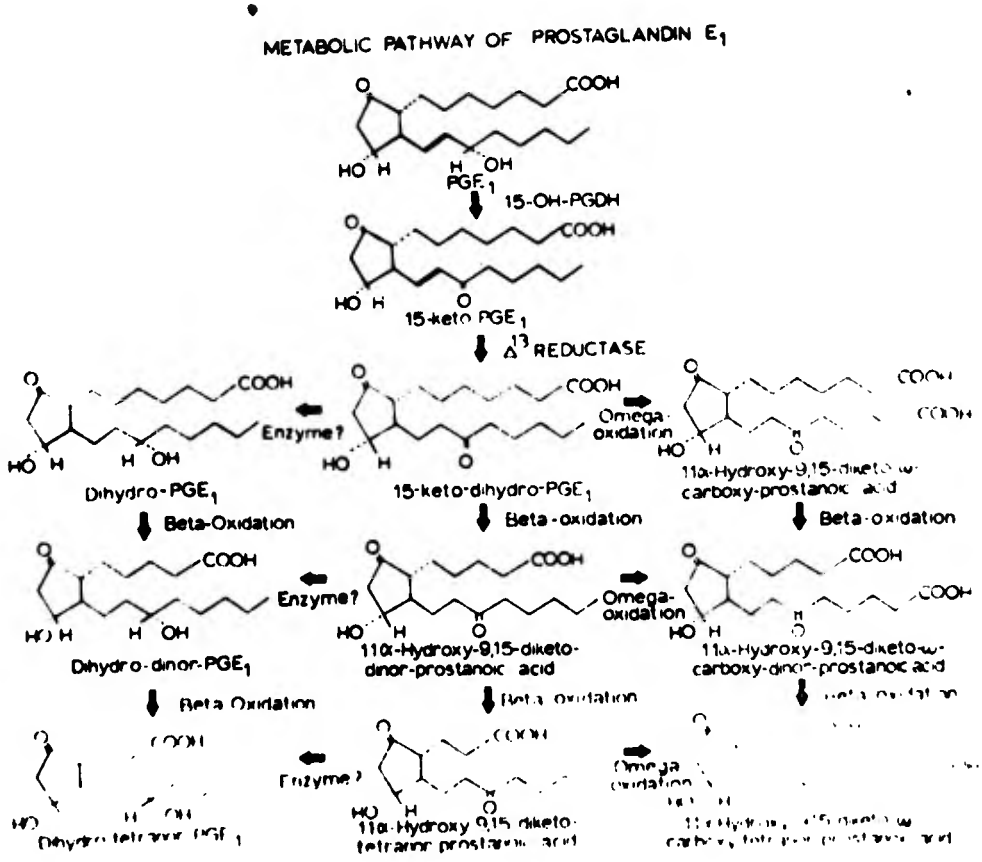

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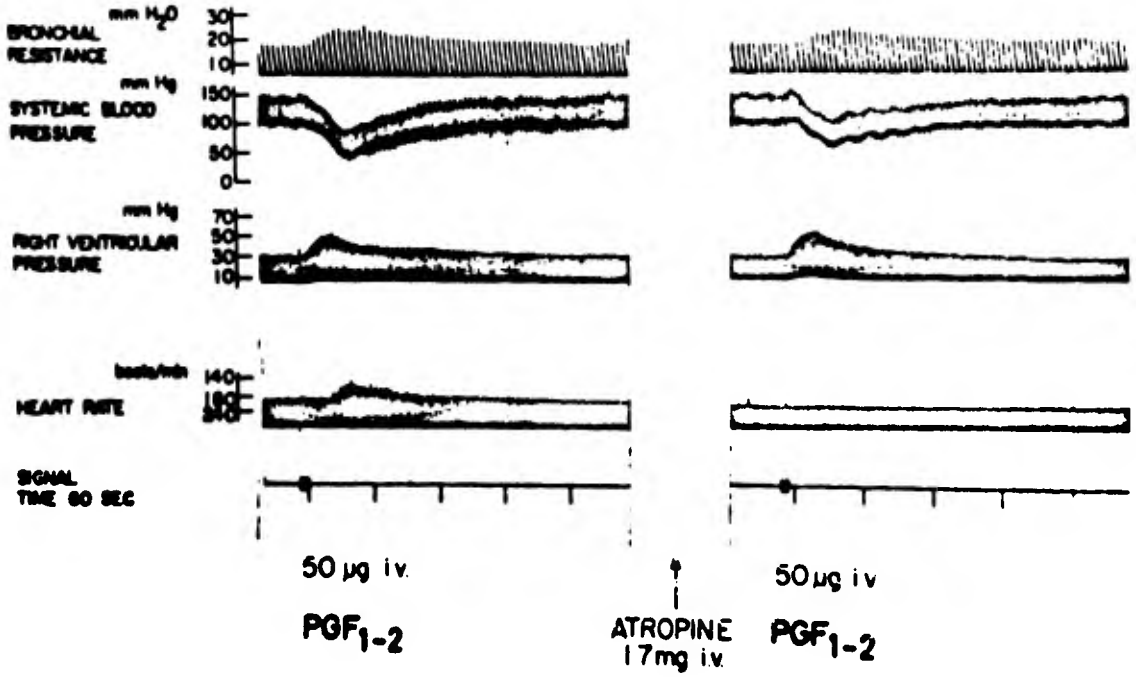

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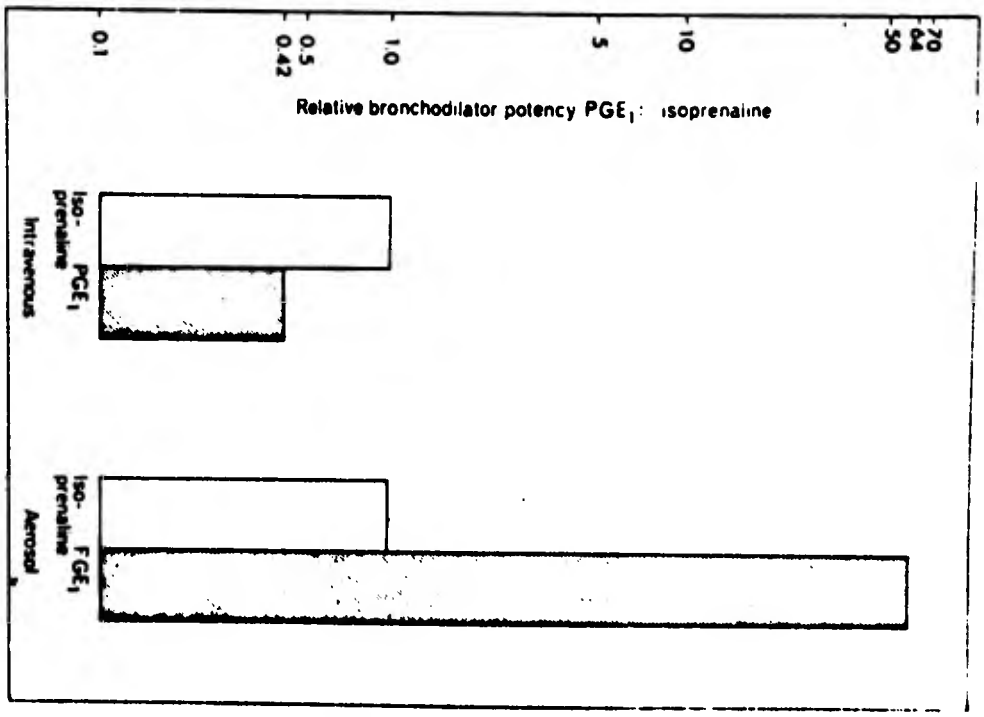

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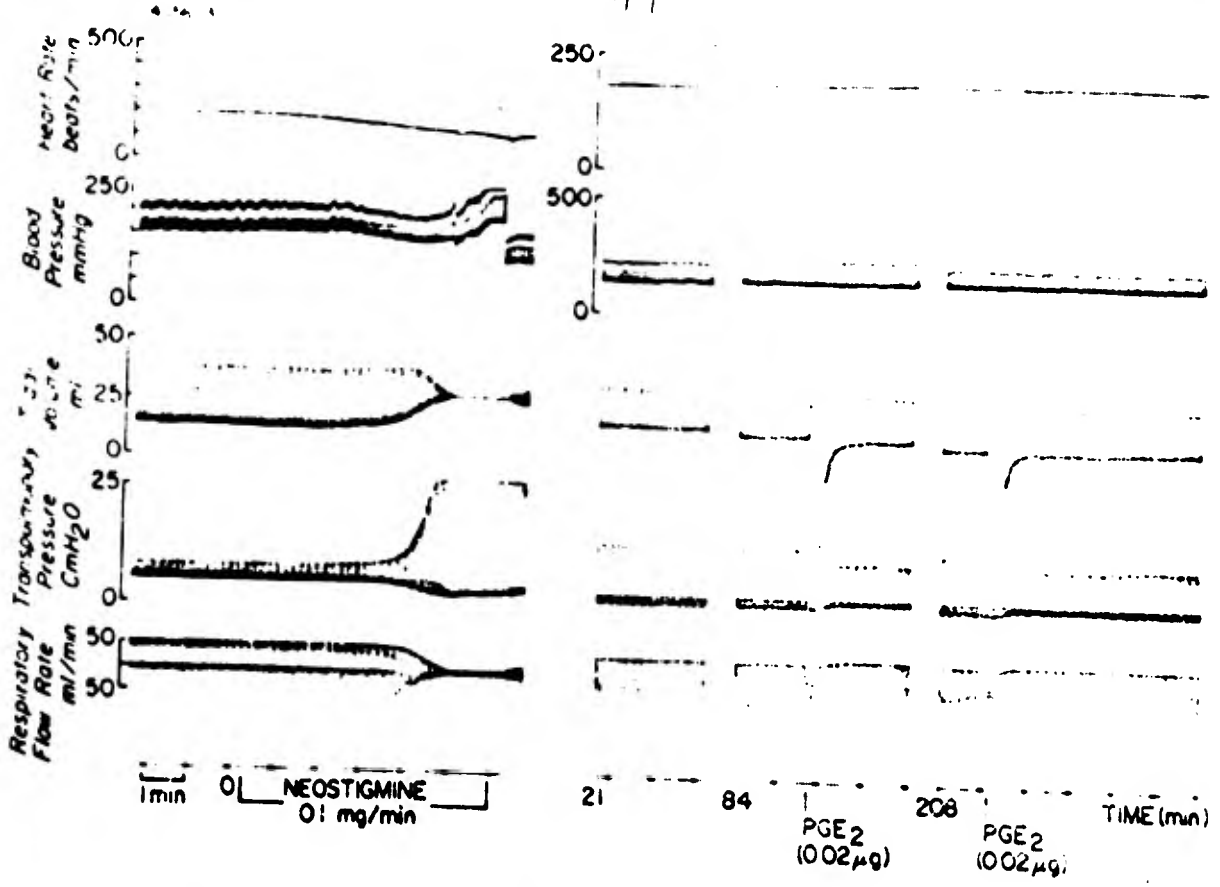

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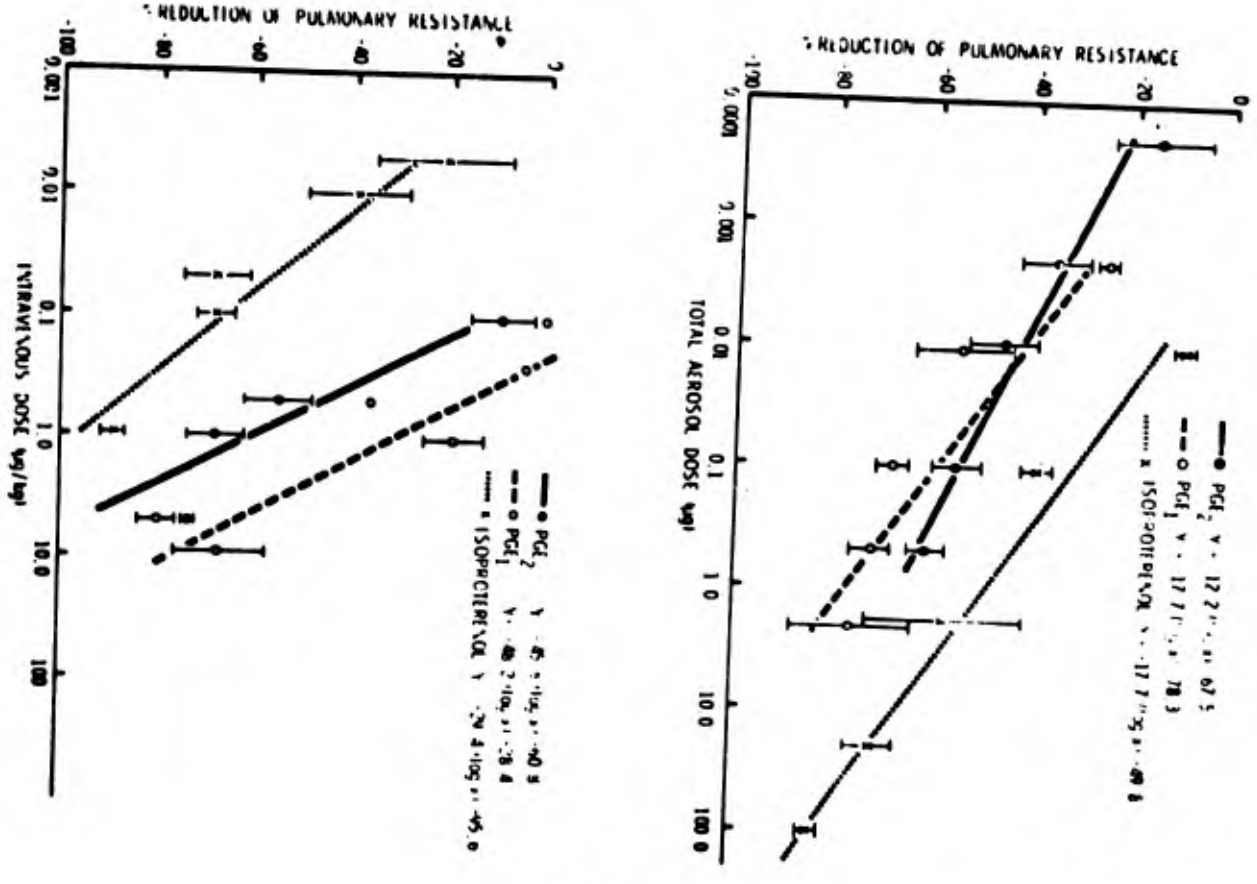


FIGURE 8

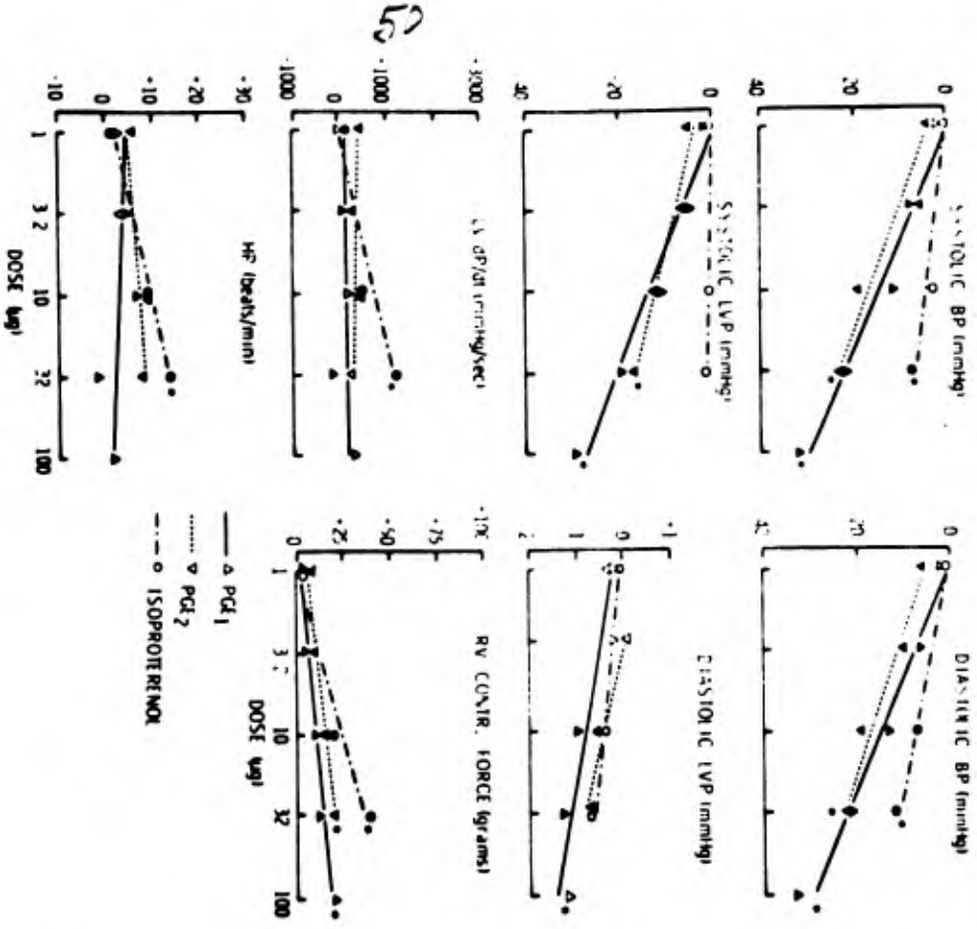


FIGURE 9

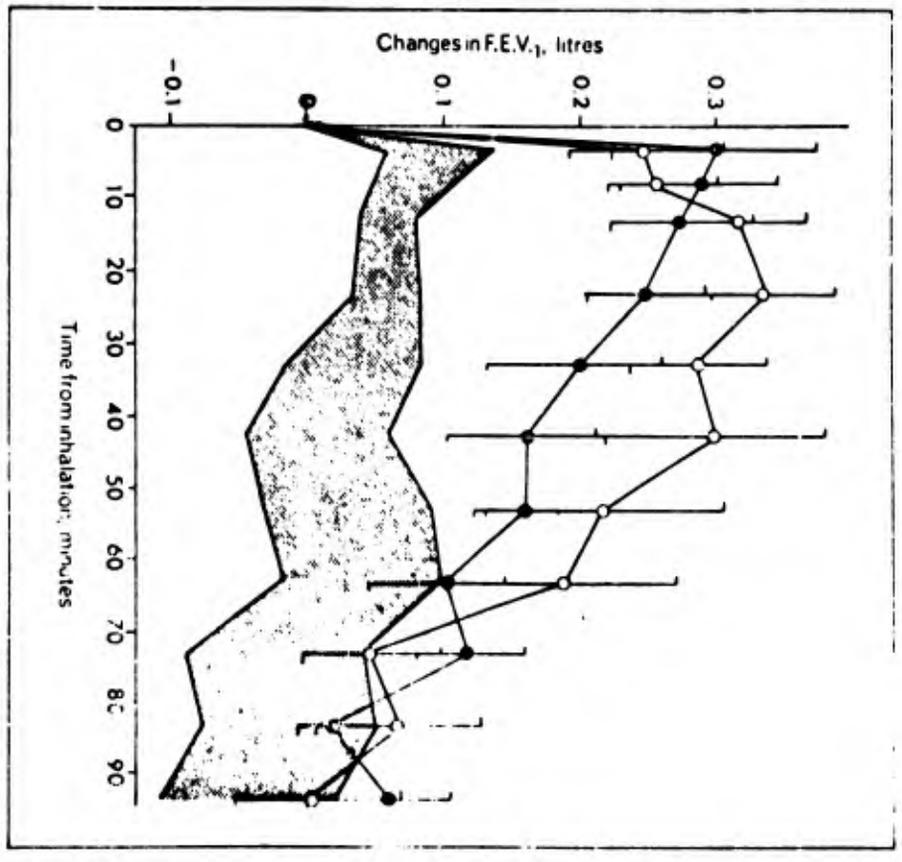


FIGURE 10

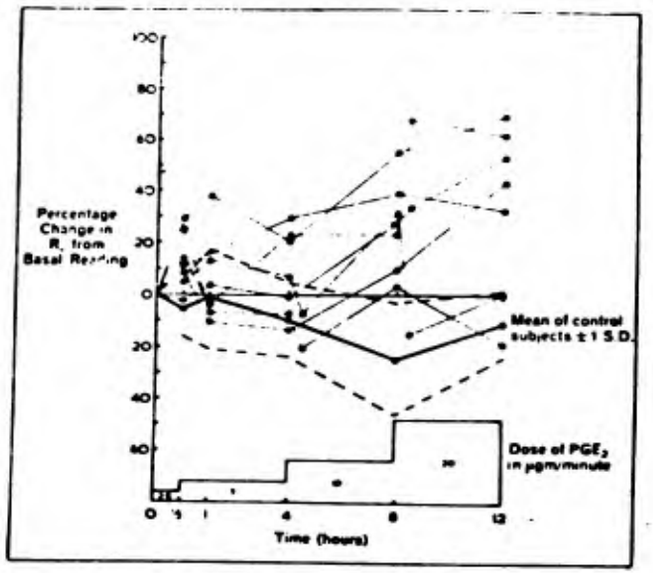
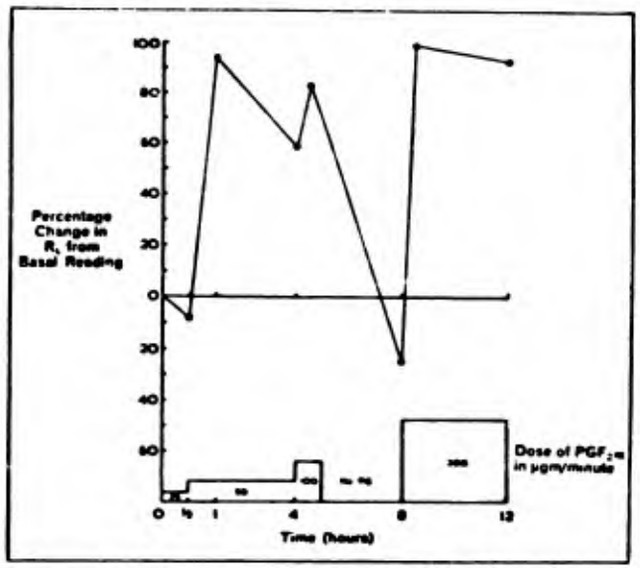


FIGURE 11



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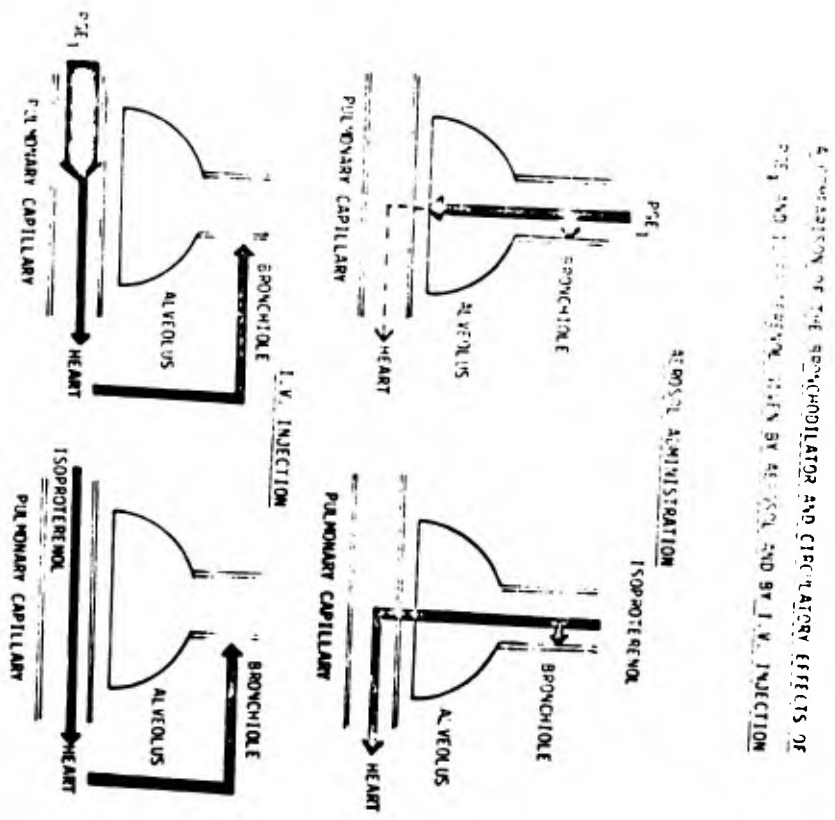

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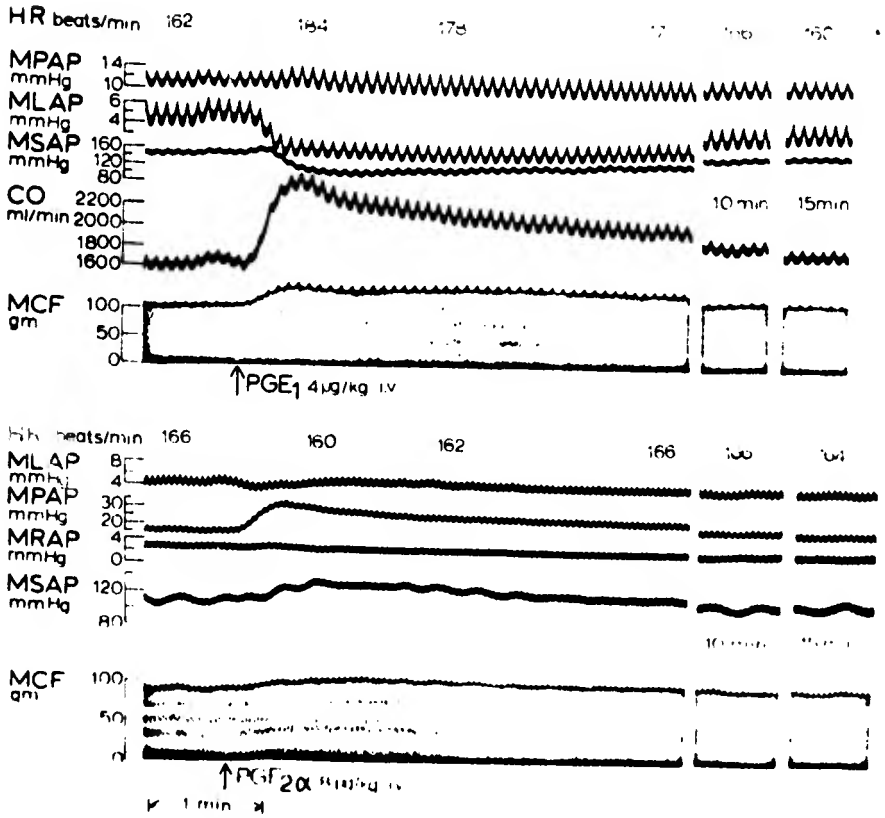
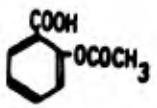


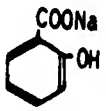
FIGURE 14

INHIBITORS OF PROSTAGLANDIN SYNTHETASE

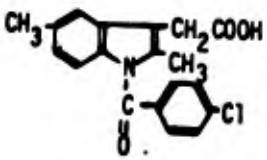
ASPIRIN



SODIUM SALICYLATE



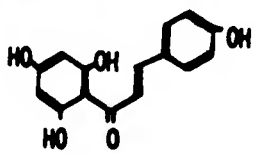
INDOMETHACINE (INDOCIN)



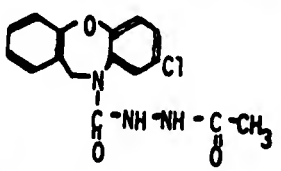
EICOSA-5,8,11,14-TETRAYNOIC ACID

PROSTAGLANDIN RECEPTOR ANTAGONISTS

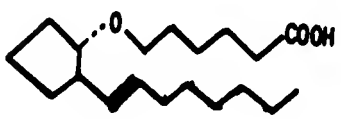
POLYPHLORETIN PHOSPHATE (PPP)



COMPOUND SU-19220(DIBENZOXAZEPINE)



7-OXA-13-PROSTYNOIC ACID



MECLOFENAMIC ACID (CI-583)

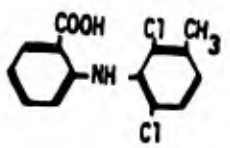


FIGURE 15