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Antagonism of prostaglandin $F_{2\alpha}$ induced bronchoconstriction and blood pressure changes by polyphloretin phosphate in the guinea-pig and cat

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Polyphloretin phosphate (PPP) when infused intravenously into guinea-pigs or cats antagonized the bronchoconstriction and blood pressure changes elicited by prostaglandin $F_{2\alpha}$ and cat paw slow reacting substance (SRS). The dose required to induce a 50% reduction was 40–80 mg/kg PPP. The effects of histamine were not significantly antagonized by the doses used. PPP itself also had a blood pressure lowering effect. The results suggest that it may act as a prostaglandin and SRS antagonist *in vivo*.

Polyphloretin phosphate (PPP)† (Diczfalusy, Fernö & others, 1953) has been reported to antagonize the stimulating action of prostaglandin E_2 (PGE_2) and prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$) on some isolated smooth muscle preparations, the blood pressure lowering effect of $PGF_{2\alpha}$ in the rabbit (Eakins & Karim, 1970; Eakins, Karim & Miller, 1970), and the increase of intraocular pressure induced by PGE_2 in the rabbit (Beitch & Eakins, 1969). Furthermore, PPP has been shown to inhibit the constricting effects of $PGF_{2\alpha}$ and slow reacting substance (SRS) on human isolated bronchi (Mathé, Strandberg & Åström, 1971; Mathé & Strandberg, 1971). These latter findings are of interest in view of the possible role of $PGF_{2\alpha}$ in anaphylactic reaction and in bronchial asthma (see Brocklehurst, 1962; Horton, 1969; Piper & Vane, 1969; Strandberg, 1971b; Hedqvist, Holmgren & Mathé, 1971). We have investigated the effects of PPP on the bronchoconstriction and on the changes in blood pressure induced by $PGF_{2\alpha}$ in the guinea-pig and cat. In a few experiments the action of PPP on SRS-induced bronchoconstriction was also examined.

MATERIALS AND METHODS

Thirty guinea-pigs (450–800 g) and 11 cats (2·2–3·5 kg) of either sex were anaesthetized with sodium pentobarbitone given intraperitoneally in doses of 60 mg/kg for guinea-pigs and 35 mg/kg for cats. The trachea was cannulated and artificial respiration established with a constant volume respirator (C. F. Palmer, London)

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† The average molecular weight of the compound was originally estimated at about 15 000. Results from recent ultracentrifugation experiments point to a value below 5000. (Files of AB Leo.)

at a rate of 48 strokes/min and stroke volume of 4–6 ml for guinea-pigs and 14–20 ml for cats according to the weight of the animal. Changes in insufflation pressure at a constant airflow were measured with a strain gauge transducer (Statham transducer model P 23 BC) connected to a side arm of the tracheal cannula. Changes in the insufflation pressure were taken to represent changes in bronchial tone (Collier, Hammond & Whiteley, 1963; Collier & James, 1967). When necessary, the expiratory arm of the tracheal cannula was briefly clamped to speed the recovery by forced inflation as previously described (Collier & others, 1963; Collier & James, 1967). Blood pressure was monitored from the left common carotid artery with a Statham transducer model P 23 AC. Both parameters were recorded on a Grass polygraph. Another catheter was inserted into a jugular vein for administration of drugs.

At the beginning of each experiment, β-adrenoceptor blockade (propranolol, i.v., 0·1 mg/kg for guinea-pig and 0·8 mg/kg for cat) was produced, since this treatment potentiates the bronchoconstriction elicited by histamine, slow reacting substance of anaphylaxis (SRS-A) and $PGF_{2\alpha}$ (Collier, James & Piper, 1965; James, 1969).

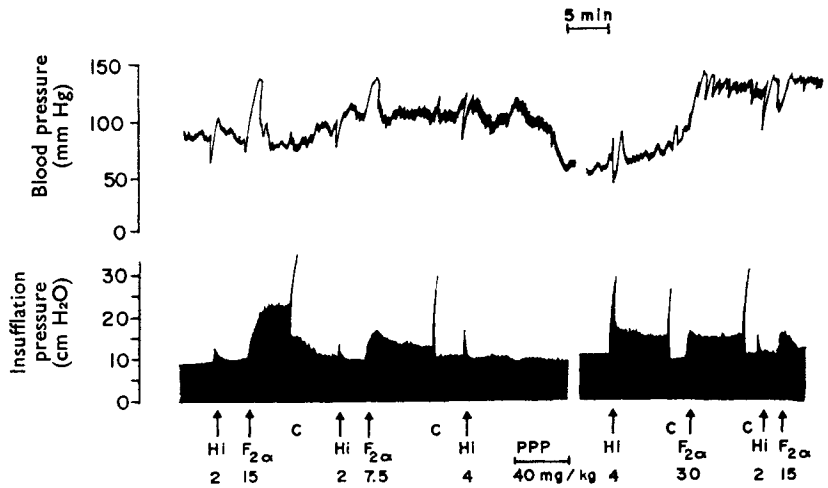

FIG. 1. Effects of i.v. injected $PGF_{2\alpha}$ and histamine (Hi) on insufflation pressure and blood pressure in an anaesthetized guinea-pig (550 g) before and after polyphloretin phosphate (PPP), 40 mg/kg. C = forced inflation.

PPP was infused over 5–15 min, whereas other drugs were given by injection. Agonists were injected alternately, before, and 5 to 65 min after the end of the PPP infusion. The magnitude of the response to an agonist after blockade with PPP was compared to that preceding the blockade, and the effect of PPP was expressed as the percent reduction of the response. Tachyphylaxis to $PGF_{2\alpha}$ was not observed. Purified, prostaglandin-free SRS was prepared by solvent extraction, silicic acid and anion exchange chromatography from effluents from cat paws perfused with compound 48/80 as described by Strandberg & Uvnäs (1971). One unit of SRS has been defined as the quantity of SRS causing, under specified conditions, the minimal measurable contraction of the guinea-pig isolated ileum (Strandberg, 1971a).

RESULTS

PPP, 40–80 mg/kg, inhibited the bronchoconstriction induced by $PGF_{2\alpha}$ (15–60 μg/kg) in both the guinea-pig and cat (Table 1). The antagonism was dose-dependent, and the intensity of blockade did not appear to change during the experimental period (65 min). The action of histamine (1–8 μg/kg) was not significantly antagonized, and immediately after the infusion of PPP—in a few instances—it even seemed to be potentiated. The effect of PPP on the bronchoconstriction induced by $PGF_{2\alpha}$ in the two species is illustrated in Figs 1 and 2.

Due to scarcity of purified SRS, experiments were conducted only on four guinea-pigs. Here PPP (40 mg/kg) reduced the bronchoconstriction induced by 250–1 000 units of SRS by 49 $\pm$ 5 (mean $\pm$ s.e.) %.

$PGF_{2\alpha}$, 15–60 μg/kg, raises the blood pressure in the guinea-pig and lowers it in the cat. The inhibitory effect of PPP on the blood pressure changes induced by $PGF_{2\alpha}$ was difficult to evaluate because PPP itself had a blood pressure lowering effect. This varied markedly; in some instances no changes were observed while in others (2 guinea-pigs but no cats) death resulted. Therefore, the antagonism was estimated only in those animals where the differences in blood pressure before and after PPP infusion were not more than $\pm$10 mm Hg. With this approach it

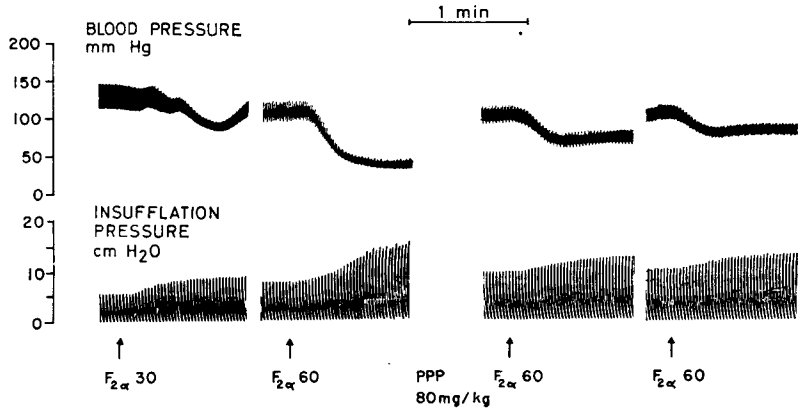

FIG. 2. Effects of i.v. injected $PGF_{2\alpha}$ on insufflation pressure and blood pressure in an anaesthetized cat (3·1 kg) before and after polyphloretin phosphate (PPP), 80 mg/kg. The intervals between the recordings were 10–15 min.

was possible to calculate the inhibitory effect of PPP in 19 of 30 guinea-pigs and in 4 of 11 cats. Table 1 shows that PPP (80 mg/kg) in both species caused about 50% inhibition of the $PGF_{2\alpha}$ effect on blood pressure. SRS, like $PGF_{2\alpha}$, produced a rise of the blood pressure in the guinea-pig. This effect also seemed to be antagonized by PPP, but because of lack of material it could not be quantitated.

The effect of PPP on the blood pressure was also investigated in 17 rats. No changes were observed using doses up to 640 mg/kg, indicating species differences in the response to PPP.

DISCUSSION

The observation of an *in vivo* inhibition of the bronchoconstricting effect of $PGF_{2\alpha}$, as well as of SRS, by PPP extends the *in vitro* findings of Mathé & others (1971) and

Table 1. *Inhibition (%) of prostaglandin $F_{2\alpha}$ induced bronchoconstriction and changes in blood pressure by polyphloretin phosphate (PPP).* Mean values and s.e. of mean. Figures in parentheses denote the number of experiments.

PPP	Bronchoconstriction		Blood pressure	
mg/kg	Guinea-pig	Cat	Guinea-pig	Cat
20	14 ± 6 (4)		2 (3)	
40	47 ± 2 (13)	10 (2)	22 ± 9 (8)	
80	85 ± 3 (13)	50 ± 3 (9)	53 ± 6 (8)	47 ± 8 (4)

Mathé & Strandberg (1971). Furthermore, changes in the blood pressure induced by $PGF_{2\alpha}$—whether a rise as in the guinea-pig or a fall as in the cat—were reduced by PPP in a dose-dependent manner.

During the work, PPP was reported to antagonize some *in vivo* effects of $PGF_{2\alpha}$ in the cat, namely the increase in intra-ilial pressure, the increase in airway resistance and the decrease in blood pressure (Villanueva, Hinds & others, 1971 and unpublished observations). Thus these authors observed effects of PPP on the action of $PGF_{2\alpha}$ in the cat similar to those seen by us. However, since dose-response relations were not the aim in their work and the doses they used were higher than ours an accurate quantitative comparison cannot be made.

The mode of action of PPP as an antagonist of prostaglandins and SRS is unknown. Previous work has suggested that PPP acts as a competitive inhibitor (Eakins & others, 1970; Mathé & Strandberg, 1971). The property of PPP to inhibit *in vitro* the action of several enzymes (e.g., hyaluronidase, phosphatases, urease) (Diczfalusy & others, 1953) does not appear to be relevant in this context (Eakins, Miller & Karim, 1971). Thus, recent experiments have shown that the inhibitory effect of PPP *in vitro* is restricted to the low molecular weight fractions in the polymer while the anti-hyaluronidase effect resides in the high molecular weight fractions (Eakins, 1971; Fex, Fredholm & others, unpublished observations).

In the concentration used to produce a 50% inhibition of the response to the agonists, PPP also lowers the blood pressure in the guinea-pig and the cat. The compound has been reported to have a similar effect on the rabbit blood pressure (Eakins & others, 1970). After infusion of PPP, we obtained a more pronounced and longlasting fall in blood pressure in the cat than was found by Villanueva & others (unpublished observations). This was probably due to our use of propranolol. Whether the blood pressure lowering property is coupled to the antagonizing action of PPP on the prostaglandin and SRS mediated effects is presently not known. If by further purification of PPP's fractions—or alternatively by a new synthesis—these two properties can be dissociated, or if topical application is feasible, a prostaglandin and SRS inhibiting drug with possible use in therapy of bronchial asthma might be developed.

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