was much larger than that caused by 1.6×10^{-4} M hydrocortisone—a concentration generally accepted as sufficient to accomplish a full block of extraneuronal uptake (Iversen & Salt 1970). This can be explained assuming that, because of its relatively high lipid solubility (Mack & Bönisch 1979), isoprenaline is able to enter the cells in part by diffusion, thus partially circumventing the block by hydrocortisone of the carrier system for the transport across the membrane. Thus, if COMT is the factor generating the concentration gradient between the biophase and the medium (Trendelenburg 1972) block of the enzyme by U-0521 will keep isoprenaline molecules for a longer time in the biophase than hydrocortisone.

This difference between the effects of U-0521 and hydrocortisone can be alternatively explained if we admit that more than one *O*-methylating system exists, only one of which is hydrocortisone-sensitive as was demonstrated for the nictitating membrane (Graefe & Trendelenburg 1974). In this case U-0521 would prolong the inactivation time more than hydrocortisone because it would block the whole *O*-methylating capacity of the tissue.

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Inhibition of antigen-induced release of prostaglandin-like material from guinea-pig trachea by antihistamines, FPL55712† and atropine

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A variety of stimuli induce the release of a prostaglandin E (PGE)-like substance from guinea-pig isolated trachea. These include histamine (Grodzinska et al 1975) and arachidonic acid (AA) as well as antigen in sensitized guinea-pigs (Burka & Paterson 1980a, b). Dexamethasone and mepacrine, both inhibitors of phospholipase A_2 (Blackwell et al 1978), inhibited the release of PGE-like material induced by histamine and antigen, but not that induced by AA, suggesting that histamine and antigen initiated prostaglandin production by providing free AA by a phospholipase A_2 mechanism (Burka & Paterson 1980b) as has been observed in guinea-pig perfused lung (Blackwell et al 1978). The present study was designed to examine by means of pharmacological antagonists whether histamine, SRS-A, or acetylcholine were responsible for the antigen-induced release of PGE-like material from guinea-pig sensitized trachea.

Male English short-hair guinea-pigs (200–250 g) were sensitized with ovalbumin 100 mg s.c. and 100 mg i.p. The trachea was removed 2–4 weeks later, spirally cut (Constantine 1965) and superfused in cascade (Vane 1964) with Krebs solution (37 °C, aerated with 95% O_2: 5% CO_2) at a flow rate of 2·5 ml min^{-1} over a rat stomach strip (Vane 1957) superfused with atropine (3×10^{-7} M), phentolamine (3×10^{-7} M), propranolol (7×10^{-7} M), mepyramine (3×10^{-7} M), methysergide (4×10^{-7} M), antagonists to cholinergic and adrenergic agents, histamine and 5-hydroxytryptamine respectively (Piper & Vane 1969), together with indomethacin (3×10^{-6} M) to prevent endogenous synthesis of PGs by the stomach strip (Eckenfels & Vane 1972). The changes in tone of both tissues were recorded isotonically with auxotonic levers (initial load 1 g for trachea and 2 g for rat stomach strip) using Harvard type 386 transducers connected to a Harvard type 350 linear chart recorder.

A dose response relationship of PGE_2 on the rat stomach strip was established and repeated throughout the experiment so that contractions of stomach strip by the effluent from the trachea could be bracketed. Differential superfusion bioassay had previously confirmed that E prostaglandins were the only biologically active AA metabolites of the cyclooxygenase pathway released from guinea-pig trachea (Grodzinska et al 1975; Burka & Paterson 1980a). The release of PGE-like material from the trachea in response to histamine, carbachol and AA was recorded in the absence and presence of drugs on the same tissue and the results were analysed by Student's *t*-test for paired data. The

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† Sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-chromene-2-carboxylate.

Table 1. The effects of antihistamines, FPL55712 and atropine on the release of PGE-like material from the guinea-pig trachea. Values are mean ± s.e.m.

Drug concn. (M)	n	PGE-like activity (ng) released from guinea-pig trachea by: Histamine 10 μg	Carbachol 10 μg	AA 5 μg or 10 μg	Ovalbamin 10 μg
Control	5	3·8 ± 0·4		12·6 ± 2·2	11·3 ± 3·3[a]
Mepyramine 10^{-6}	5	0·0 ± 0·0***		13·8 ± 2·2	0·4 ± 0·4**
Control	4	5·8 ± 1·7		13·5 ± 3·8	
Diphenhydramine 10^{-5}	4	0·0 ± 0·0***		20·0 ± 0·0**	4·3 ± 2·5
Control	5	1·7 ± 0·3		7·4 ± 0·8	
Chlorpheniramine 10^{-5}	5	0·0 ± 0·0***		20·0 ± 0·0**	2·3 ± 0·6*
Control	4	1·8 ± 0·3		11·5 ± 4·9	
Cimetidine 10^{-5}	4	6·0 ± 2·3		5·5 ± 2·5	5·5 ± 2·5
Control	9	2·5 ± 0·7		9·4 ± 1·8	
FPL55712 $1·7 \times 10^{-6}$	5	2·7 ± 0·9		14·0 ± 2·5	6·4 ± 3·9
$5·2 \times 10^{-6}$	4	1·5 ± 0·3		14·3 ± 3·3	1·6 ± 0·2*
Control	10	1·6 ± 0·5	1·6 ± 0·5	2·0 ± 0·3	
Atropine 10^{-6}	5	2·8 ± 0·5*	0·8 ± 0·1***	4·4 ± 0·2**	0·7 ± 0·5**
10^{-5}	5	2·0 ± 0·7	0·0 ± 0·0***	4·7 ± 0·8**	0·0 ± 0·0**

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·005$.
[a] All controls (n = 8) for ovalbumin were carried out on tracheae that were not drug-pretreated.

response to ovalbumin was measured in different tracheae and analysis carried out by Student's *t*-test for unpaired data.

Mepyramine (10^{-6} M), diphenhydramine (10^{-5} M) and chlorpheniramine (10^{-5} M) are all effective inhibitors of the contraction induced by histamine (10^{-4} M) on guinea-pig trachea (Burka & Paterson, submitted for publication) and similarly inhibit the release of PGE-like material induced by histamine (Table 1). The H_1-receptor antagonists did not inhibit the release of PGE-like material induced by AA, suggesting that histamine acts on a phospholipase to free AA from phospholipids. In fact, diphenhydramine and chlorpheniramine enhanced the release of PGE-like material induced by AA. The release of PGE-like material induced by ovalbumin from sensitized tracheae was reduced significantly by mepyramine and chlorpheniramine. This suggests that histamine released during antigen challenge of sensitized trachea contributes to the release of PGE-like material. The effects of histamine on the release of PGE-like material are mediated via H_1-receptors since the H_2-receptor antagonist, cimetidine had no significant effect on the release of PGE-like material induced by histamine, AA or ovalbumin.

The selective SRS-A antagonist, FPL55712 (Augstein et al 1973) did not influence the release of PGE-like material induced by histamine or AA, but reduced the release induced by ovalbumin, implying that immunologically-released SRS-A also contributes to the release of PGE-like material.

Atropine reduced the release of PGE-like material induced by carbachol and ovalbumin, but slightly enhanced the release induced by histamine and AA. The mechanism of the enhancement is not known. Berti et al (1980) recently found that atropine inhibited the thromboxane A_2 generation initiated by administration of histamine or SRS-A into guinea-pig isolated perfused lungs, yet carbachol alone did not induce PG or thromboxane release. In contrast, our experiments demonstrate that trachea can generate PG-like material when muscarinic receptors are stimulated by carbachol. However, since it is not known whether acetylcholine is released from nerve terminals after in vitro antigen challenge of sensitized trachea, the mechanism of inhibition of ovalbumin-induced release of PGE-like material by atropine is uncertain. It is unlikely to involve the phospholipase A_2 interference postulated by Berti et al (1980) since histamine-induced release of PGE-like material from the trachea is not inhibited by atropine.

These studies demonstrated that mediators, such as histamine and SRS-A, released during an allergic reaction are capable of releasing PGE-like material. However, since responses of trachea to exogenous PGE_2 are weak, unpredictable and inconsistent (Burka & Paterson 1980b), it is unlikely that PGE plays a major regulatory role. Grodzinska et al (1975) have suggested that PGE is released as a local defence mechanism protecting against strong constriction of the airways, but the amount released is probably insufficient to overcome the powerful effects of the released mediators.

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