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ANAPHYLACTIC CONTRACTION OF PULMONARY BLOOD VESSELS OF CHICKEN

N. CHAND & P. EYRE

Pharmacology Laboratory, Department of Biomedical Sciences, University of Guelph, Guelph, Ontario N1G 2W1, Canada

1 Isolated pulmonary arterial and vein strips from sensitized or non-sensitized chickens exhibited dose-dependent contractions to adrenaline >, noradrenaline >, 5-hydroxytryptamine >, histamine >, dopamine. Individual variability in the responsiveness of the vessels to agonists was marked. In general veins were 2 to 25 times more sensitive to agonists than arterial strips.

2 Isoprenaline (a relatively specific β-adrenoceptor agonist) induced relaxations of the submaximally contracted pulmonary vein and arteries at low doses and contractions at high concentrations.

3 Contractile responses to acetylcholine or carbachol were not regularly recorded; only 50% of the vessels reacted to cholinoceptor agonists over a wide threshold dose range.

4 Chicken pulmonary vessels were found relatively insensitive to bradykinin.

5 Effects of prostaglandins were variable. Prostaglandin $F_{2\alpha}$ induced dose-related contractions of the vein and arterial strips; prostaglandins E_1 and E_2 at low doses relaxed partially contracted pulmonary artery irrespective of the spasmogen used and further increase in doses induced either no effect or contractions. Prostaglandin E_1 induced marked and rapid contractions of the vein. Prostaglandin E_2 induced relaxations of the prostaglandin $F_{2\alpha}$-contracted vein only, but produced no effect or slight contractions of the veins partially contracted to other spasmogens.

6 Pulmonary arterial and vein strips obtained from chickens sensitized to horse plasma exhibited Schultz-Dale contractions of variable magnitude and duration to specific antigenic challenge only. In many vessels, antigen-induced contractions were associated with marked increase in spontaneous activity.

7 The importance of the Schultz-Dale reaction in avian pulmonary vessels is discussed in relation to the right heart dilatation associated with anaphylaxis in the chicken.

Introduction

Specific antigen-induced contraction of smooth muscle taken from sensitized tissue is known as a Schultz-Dale phenomenon (Schultz, 1910; Dale, 1913). This immunopharmacological reaction has subsequently been demonstrated in numerous tissues: the guinea-pig ileum (Dale & Okpako, 1969; Dale & Zilleti, 1970; Cîrstea, 1970; Okpako, 1970) and trachea (Sörenby, 1975); rat uterus (Kellaway, 1930); human tracheal and bronchial strips (Schild, Hawkins, Mongar & Herxheimer, 1951; Schild, 1956); pulmonary artery of the rabbit (Lecomte, 1958) and calf (Eyre, 1970; 1975); calf pulmonary veins (Eyre, 1970; 1971a; 1973; 1975; Eyre & Deline, 1971a, b; 1972), hepatic veins (Holroyde & Eyre, 1975) and digital veins (Elmes & Eyre, unpublished); pulmonary vein of the horse (Eyre, 1972; Burka, Deline, Holroyde & Eyre, 1976) and recently several gastrointestinal tissues of the domestic fowl (Chand & Eyre, 1976). Surprisingly, sheep pulmonary vein has been shown to relax to antigen (Eyre, 1975).

Sensitized adult domestic fowl exhibit antigen-dose-dependent increases in the central venous pressure associated with systemic arterial hypotension (Chand & Eyre, unpublished). Birds that die in anaphylaxis show right heart dilatation (Lecomte & Beaumariage, 1958; Aronson, Bilstad & Wolfe, 1961; Chand & Eyre, unpublished) which has also been described as a common feature of systemic anaphylaxis in man, mouse rabbit and chicken; attributable to increased pulmonary vascular resistance (Aronson *et al.*, 1961).

Thus, it was important to investigate the possibility of demonstrating the Schulz-Dale reaction in pulmonary blood vessels of chickens and to study the effects of catecholamines, 5-hydroxytryptamine, acetylcholine, histamine, bradykinin and prostaglandins at the same time.

Methods

Adult domestic fowl (White Leghorn) weighing 2 to 4 kg, were sensitized to horse plasma (1 ml/kg, i.v.)

(Chand & Eyre, 1976). On the 7th day after sensitization, chickens were killed with pentobarbitone sodium. Immediately, combined heart and lungs were carefully removed and kept in aerated ice cold Krebs solution. Probes of appropriate diameter were passed into the pulmonary artery and vein from their points of cardiac origin. The vessels were carefully detached from surrounding lung tissues and then cut helically following the method of Furchgott & Bhadrakom (1953) to give a strip of about 2 cm length and 2 to 3 mm width containing predominantly circular smooth muscle fibres. Arterial and venous strips from individual chickens were suspended in 30 or 50 ml organ baths containing Krebs-Henseleit solution maintained at 37°C, bubbled with 5% CO_2 in O_2. Tissues were allowed to equilibrate for 1 h under a resting tension of 0.5 g for pulmonary vein and 1 g for pulmonary artery. Pulmonary vessel strips from unsensitized chickens were set up in the same way.

Three or four reproducible responses (single or cumulative) of each strip to 3 or 4 agonists at 15 to 30 min intervals were recorded with an E & M isotonic myograph transducer connected to an E & M Desk Model, 4-Channel Physiograph (DMP-4B) pen recorder (Narco Instruments, Houston, Tex.). The strips were then 'challenged' with 0.2 to 0.3 ml of horse plasma. In some experiments, after first challenge, strips were washed 2–3 times and challenged within 15–30 min with a second identical dose of antigen to study the extent of desensitization. Subsequently, the strips were washed and allowed to rest for 1 to 3 hours. Responsiveness to one or more agonist(s) was checked and the tissues were again challenged with antigen to study the extent of recovery of the Schultz-Dale response.

Drugs

The following drugs were used: histamine diphosphate, serotonin creatinine sulphate (5-hydroxytryptamine, 5-HT), bradykinin triacetate, carbamylcholine chloride (carbachol), acetylcholine chloride (ACh), adrenaline bitartrate, noradrenaline bitartrate, dopamine hydrochloride, (Nutritional Biochemical Corp., Cleveland, Ohio), isoprenaline hydrochloride, (Wintrobe, New York) and prostaglandins E_1, E_2 and $F_{2\alpha}$ (gifts from Upjohn Co., Kalamazoo, Mich.).

Results

Vascular reactivity to drugs

Pulmonary artery and pulmonary vein of the fowl exhibited dose-dependent contractions to adrenaline, noradrenaline, 5-HT, dopamine, histamine, ACh, carbachol and prostaglandin $F_{2\alpha}$. Vein strips were 2 to 25 times more reactive than artery strips to most of the agonists tested. Threshold dose-ranges to agonists

Table 1 The threshold dose-ranges of some vasoactive substances on isolated spiral strips of pulmonary artery and vein of adult domestic fowl

Vasoactive substances	*Threshold dose-ranges (M)* *Pulmonary artery*	*Pulmonary vein*
Histamine	10^{-5} to 5×10^{-4}	10^{-6} to 10^{-4}
5-Hydroxytryptamine	5×10^{-8} to 10^{-5}	10^{-8} to 10^{-5}
Acetylcholine	5×10^{-6} to 10^{-4}	10^{-5} to 5×10^{-4}
Carbachol	10^{-7} to 10^{-4}	10^{-5} to 10^{-4}
Adrenaline	2×10^{-8} to 5×10^{-7}	10^{-9} to 2×10^{-7}
Noradrenaline	5×10^{-8} to 5×10^{-7}	5×10^{-9} to 2×10^{-7}
Dopamine	2×10^{-6} to 10^{-5}	10^{-6} to 5×10^{-6}
Isoprenaline	10^{-8} to 10^{-7} R 10^{-6} to 10^{-5} C	10^{-8} to 10^{-7} R 10^{-6} to 10^{-5} C
Bradykinin μg/ml	10 to 50	10 to 50
PGE_1 ng/ml	10 to 500 R	50 to 500 C
μg/ml	2 to 5 C	
PGE_2 ng/ml	10 to 100 R	10 to 100 R[1]
μg/ml	2 to 5 C	1 to 5 C
$PGF_{2\alpha}$ μg/ml	0.1 to 1 C	0.1 to 0.5
* Horse plasma (ml/50 ml)	0.01 to 0.1	0.01 to 0.1

* Only on sensitized tissues; R = Relaxation of blood vessel strips partially contracted to histamine, 5-HT, catecholamines, prostaglandins or antigen. R[1] = Relaxation of only prostaglandin $F_{2\alpha}$-contracted vein; C = Contraction.

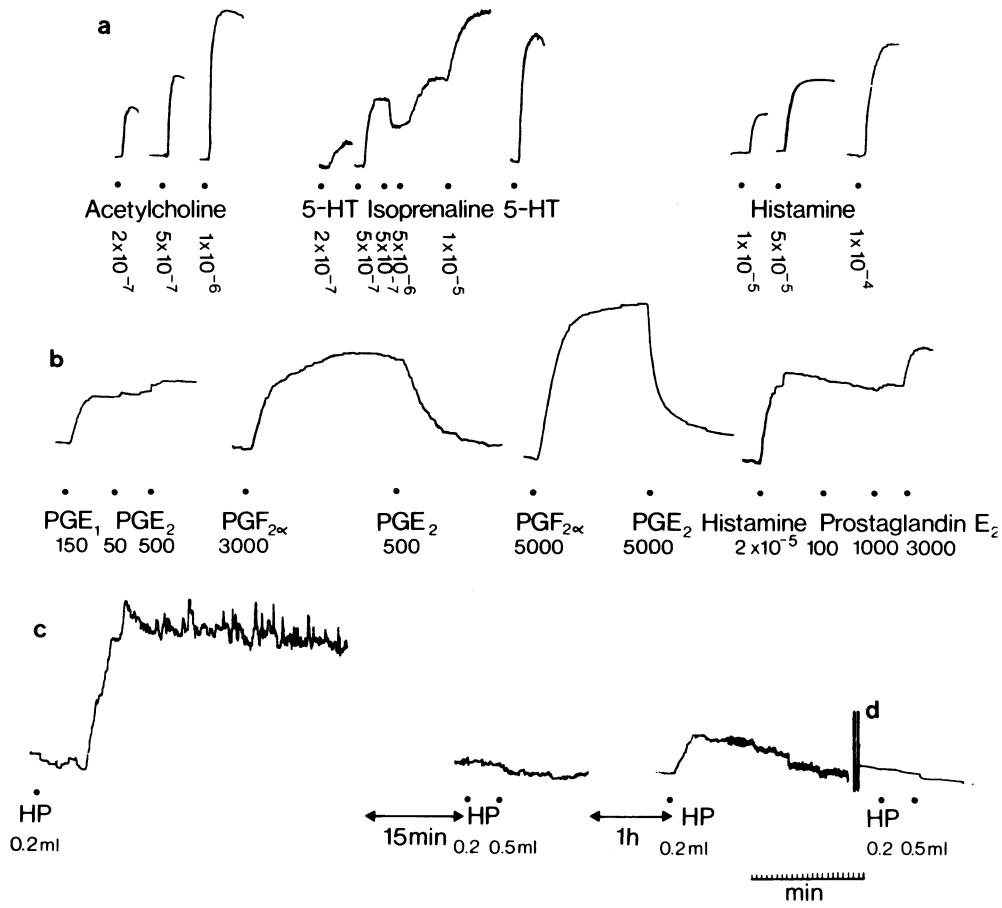

Figure 1 Three (a, b and c) isolated spiral stips of pulmonary veins of sensitized adult domestic fowl. Strip (a) shows typical dose-related contractile responses to acetylcholine, 5-hydroxytryptamine (5-HT) and histamine; also relaxant effect of low dose of isoprenaline on partially 5-HT-contracted vein, and contraction to higher doses of isoprenaline. Strip (b) shows contractile responses to prostaglandins E_1, and $F_{2\alpha}$(PGE_1, $PGF_{2\alpha}$) and histamine. PGE_1-contracted vein is further contracted by prostaglandin E_2 (PGE_2). $PGF_{2\alpha}$-contracted vein is relaxed by PGE_2 in dose-dependent fashion. Histamine-contracted vein is further contracted by high doses of PGE_2. Strip (c) shows a Schultz–Dale anaphylactic reaction to specific sensitizing antigen (horse plasma). Subsequent challenge to the same antigen after 15 min exhibits desensitization. Allowing the strip to 'rest' for 1 h with frequent washing results in partial recovery of anaphylactic response. Additional strips (d) obtained from nonsensitized chickens, exhibited similar responses to agonists as sensitized strips, but did not contract to even higher doses of horse plasma. Time marker indicates minutes. Concentrations of agonists are molar bath concentrations except prostaglandins which are ng/ml. Horse plasma (HP) ml per 50 ml bath.

presented in Table 1, clearly show considerable variability in reactivity to the drugs tested. Characteristic responses to ACh, histamine, 5-HT and prostaglandins are shown in Figures 1 and 2 (a and b). Many vein (7/15) and arterial (5/17) strips did not react to ACh or carbachol (10^{-5} to 10^{-3} M), while others exhibited dose-dependent (10^{-7} to 10^{-5} M) rapid contractions.

Histamine was found to be 100 to 1000 times less active than 5-HT, noradrenaline or adrenaline. Some (4/15) pulmonary arterial strips were 2 to 15 times more responsive to histamine than the corresponding veins. A few of the veins (4/18) and arterial (5/15) strips exhibited extremely low reactivity to histamine (threshold $> 10^{-4}$ M).

Although vein strips were generally more responsive than arteries to 5-HT, in some cases (5/23) the arteries were the more responsive. 5-HT,

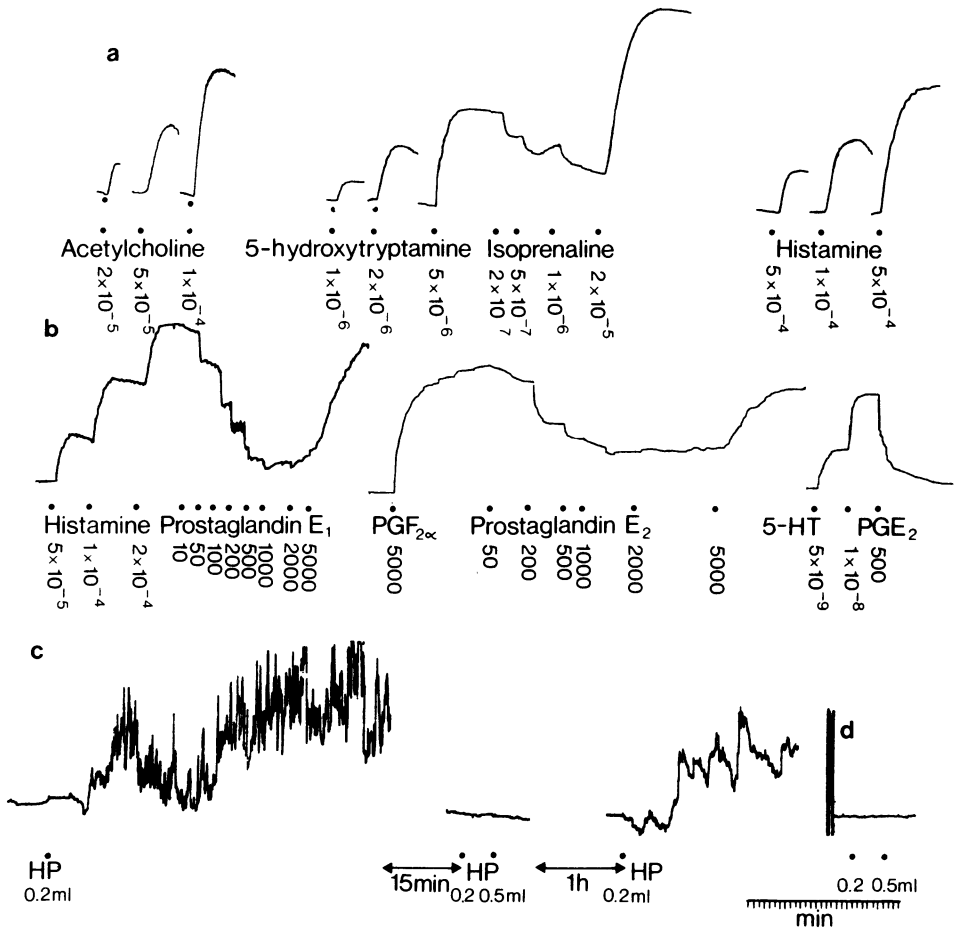

Figure 2 Three (a, b and c) spiral stips of pulmonary arteries of sensitzed adult domestic fowl. Strip (a) shows dose-dependent contractions to acetylcholine, 5-hydroxytryptamine (5-HT) and histamine: also relaxant effect of low doses of isoprenaline on 5-HT-contracted artery, and contraction by further increase in dose of isoprenaline. Strip (b) exhibits relaxant effects of prostaglandins E_1 and E_2 (PGE_1 and E_2) on partial contraction by histamine, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and 5-HT. Higher concentrations of both PGE_1 and E_2 induce contractive responses. Strip (c) demonstrates a Schultz–Dale anaphylactic reaction associated with marked increase in spontaneous activity. Second antigenic challenge induces desensitization. Allowing the strip to rest for 1 h after frequent washings and challenging with antigen induces partial recovery of anaphylactic response. Additional arterial strips (d) obtained from nonsensitized chicken, showed similar agonist responses to the sensitized strips but showed no response to horse plasma even at higher doses. Time marker indicates minutes. Concentrations of agonists are molar bath concentrations except prostaglandins which are ng/ml Horse plasma (HP), ml per 50 ml bath.

adrenaline and noradrenaline were approximately equieffective. Dopamine however was 100 to 1000-fold less potent than the other catecholamines.

Isoprenaline (10^{-8} to 5×10^{-6} M) produced dose-related relaxations of pulmonary veins and arteries that were partially contracted to histamine, 5-HT, prostaglandin $F_{2\alpha}$ or horse plasma. Further increase in the isoprenaline concentration (10^{-5} to 5×10^{-5} M) induced dose-dependent contractions. Arterial preparations were consistently more sensitive than veins to isoprenaline (Figures 1a & 2a).

Bradykinin (1 to 50 μg/ml) tested on a limited number of veins ($n=4$) and arteries ($n=5$) exhibited weak contractile responses subject to tachyphylaxis.

Prostaglandin $F_{2\alpha}$ (0.1 to 10 μg/ml) produced dose-dependent contractions of both artery and vein strips.

Effects of prostaglandins E_1 and E_2 were variable. Arterial strips that were contracted submaximally to histamine, 5-HT, prostaglandin $F_{2\alpha}$, carbachol or antigen were relaxed by prostaglandins E_1 and E_2 (10 to 1000 ng/ml) in dose related fashion; further increase in the concentrations (1 to 10 μg/ml) produced either no effect or contractile responses of variable magnitude (Figure 2b).

Prostaglandin E_1 (50 ng to 5 μg/ml) always produced dose-dependent contractions of the pulmonary vein. Prostaglandin E_2 (100 ng to 5 μg/ml) caused dose-related relaxations in prostaglandin $F_{2\alpha}$-contracted vein strips only and showed no effect or slight contractile responses of veins contracted by prostaglandin E_1. In contrast, prostaglandin E_2 produced further contraction of veins that were partially contracted to histamine and 5-HT (Figure 1b).

Schultz–Dale response

The incidence of Schultz–Dale reactions in pulmonary blood vessels of chicken is given in Table 2. Vessels obtained from non-sensitized chickens exhibited responses to agonists similar to those of sensitized birds, but none of the control veins ($n=6$) or arteries ($n=7$) contracted to horse plasma (0.2 to 0.5 ml in 30 to 50 ml bath). Sixty-five % of pulmonary arteries and 76% of the veins obtained from chickens sensitized to horse plasma contracted to 0.2 ml horse plasma but did not react to non-specific antigens (bovine plasma, duck plasma, crystalline albumins of dog, cow, rabbit) over wide dose-ranges. The character of the Schultz–Dale response was variable with respect to the latent period (30 s to 5 min), duration (5 to 30 min), magnitude (10–90% of the maximum) and degree of spontaneity. Increased spontaneous activity was seen in 50% of the vessels. No correlation could be found between vascular reactivity to agonists and antigen. Some strips weakly sensitive to histamine, 5-HT or carbachol (10^{-5} to 10^{-4}M) reacted strongly to specific antigen. In a few, the reverse of this was found. The second antigen 'challenge' with the same or higher dose 15 to 30 min after the first challenge, produced either no response or markedly reduced reaction. After allowing the strips to 'rest' for 1 to 3 h there was no change in reactivity to agonists, but partial recovery in responsiveness to the antigen (Figures 1 and 2, c) was recorded.

Discussion

In this study most of the pulmonary vein and artery strips of the chickens contracted dose-dependently to catecholamines, histamine, 5-HT, ACh and carbachol. Earlier Somlyo, Somylo & Woo (1967) reported that pulmonary arterial strips of adult fowl are insensitive to ACh, histamine, 5-HT and bradykinin. The reasons for this discrepancy are difficult to assess but may be associated with differences in age and breed. The variations and irregular responses of avian pulmonary vessels to ACh and carbachol were not surprising, since similar findings have been noted earlier with bovine pulmonary (Burka & Eyre, 1974), mesenteric, hepatic (Holroyde & Eyre, 1975), and digital vessels (Elmes & Eyre, unpublished).

Isoprenaline produced dose-dependent relaxations of both pulmonary artery and vein at low doses and contractions at higher doses. Similar responses to isoprenaline have earlier been shown in the avian anterior and posterior mesenteric and pancreaticoduodenal veins (Bolton & Bowman, 1969), rabbit aorta (Furchgott & Bhadrakom, 1953), calf mesenteric vein (Holroyde & Eyre, 1975) and pulmonary artery and vein (Eyre, 1971b). In some of the blood vessels a complete lack of β-adrenoceptor (inhibitory adrenergic) mechanisms has been reported (Somlyo & Somlyo, 1970). The possible explanations for the dual responses to isoprenaline (a specific β-adrenoceptor agonist) may be the presence of fewer β-inhibitory receptor sites eliciting relaxations. When all these sites are occupied, the drug may activate α-adrenoceptors and induce contractile responses.

Table 2 Incidence of Schultz–Dale reactions in pulmonary blood vessels of the adult chickens

	Pulmonary artery	*Pulmonary vein*
Non-sensitized		
Positive reactors	0/7	0/6
Sensitized		
Positive reactors	15/23 (65%)	13/17 (76%)
I. Strong contractions (50–90% max,)	5/23	4/17
II. Intermediate contractions (25–50% max.)	7/23	5/17
III. Weak contractions (10–25% max.)	3/23	4/17

This would indicate relatively poor specificity of isoprenaline on certain blood vessels (Eyre, 1971b; Holroyde & Eyre, 1975; Elmes & Eyre, unpublished) and/or may suggest relatively greater intrinsic activity at α-adrenoceptors (Ariens, 1954) in this system.

The insensitivity of avian pulmonary vessels to bradykinin supports similar findings by Somlyo *et al.* (1967). This may at least in part be attributed to chemical differences between the avian kinins (ornithokinins) and other kinins (Eisen, 1971).

The effects of different prostaglandins on isolated vascular smooth muscles have been reported to vary greatly with the species, vascular bed and tone of the vessels (Joiner, Kadowitz, Hughes & Hyman, 1975). Prostaglandin $F_{2\alpha}$ induced dose-dependent contractions of the avian pulmonary vein and artery. Similar contractile responses to prostaglandin $F_{2\alpha}$ have been reported earlier on various blood vessel strips (Hiller & Karim, 1968; Lewis & Eyre, 1972; Burka & Eyre, 1974; Joiner *et al.*, 1975). Low doses of prostaglandin E_1 and E_2 induced relaxation of avian pulmonary arterial strips irrespective of the spasmogen used; a further increase in the concentrations of E_1 and E_2 induced contractions of variable magnitudes. Similar biphasic effects have been reported for prostaglandin E_1 and E_2 on small mesenteric and renal arteries of cats, dogs and rabbit (Strong & Bohr, 1967) and prostaglandin E_2 on bovine pulmonary vein (Burka & Eyre, 1974).

Prostaglandin E_1 caused strong contractions of pulmonary veins of chickens, while prostaglandin E_2 induced reversal of only prostaglandin $F_{2\alpha}$-induced contractions, and produced either no effect or slight contractions of veins partially contracted to other spasmogens.

The pulmonary vessels of the chickens may now be added to the list of vascular tissues showing the Schultz–Dale reaction, e.g. pulmonary vessels of rabbit (Lecomte, 1958), calf (Eyre, 1970; 1971a; 1973; 1975; Eyre & Deline, 1971a, b; 1972), horse (Eyre, 1972; Burka *et al.*, 1976); and the hepatic (Holroyde & Eyre, 1975) and digital (Elmes & Eyre, unpublished) veins of the calf.

The considerable variability in the latent period, duration, magnitude and spontaneity of Schultz–Dale reaction of chicken pulmonary vessels may possibly be atributed to different degrees of hypersensitivity of the tissues to the sensitizing antigen; the number of the mast cells; the amount of vasoactive substances in the mast cells and to physical differences, i.e. proportional distribution of cardiac, circular and longitudinal muscle fibres, amount of the adherent lung tissue. Similar variations were also found with several gut tissues of birds exhibiting the Schultz-Dale reaction (Chand & Eyre, 1976).

In this study the following criteria, characteristic of Schultz–Dale phenomenon, were satisfied: (i) tissue from non-sensitized chickens did not react to specific sensitizing antigen even at high bath concentrations; (ii) tissues from sensitized birds did not react to heterologous or homologous non-specific antigens; (iii) specific antigen-induced contractions were invariably preceded by a latent period of at least 30 s: probably indicative of antigen-antibody reaction and formation and release of vasoactive substances (histamine, 5-HT, prostaglandins, slow reacting substance of anaphylaxis (SRS-A), etc.) from the mast cells; (iv) tachyphylaxis or desensitization to second antigenic challenge, a phenomenon reported earlier by several workers (Kellaway, 1930; Schild *et al.*, 1951; Schild, 1956; Dale & Okpako, 1969; Okpako, 1970, Eyre, 1970; 1971a; Holroyde & Eyre, 1975; Chand & Eyre, 1976); (v) partial recovery of the antigen responses after 1 to 3 h of resensitization 'rest' interval.

Some of sensitized avian pulmonary vessels did not respond to antigen. It has previously been reported that the Schultz–Dale reaction does not always occur in all vascular strips (Eyre, 1970; Eyre & Deline, 1971b; 1972; Holroyde & Eyre, 1975).

Among several possibilities put forward to explain the Schultz–Dale phenomenon the most acceptable hypothesis is the interaction of the antigen with the tissue-fixed antibodies on the mast cells leading to a series of enzymatic reactions resulting in the changes in cell permeability and extrusion (exocytosis) of stored granules of mediators of immediate hypersensitivity and activation of synthesis release of other vasoactive lipids (prostaglandins, RCS, SRS-A, etc.) (Feldberg, 1961; Dale & Zilletti, 1970).

The evidence suggests that *in vitro* anaphylactic contractions of avian pulmonary vessels may not be mediated by histamine. The chicken lung contains few mast cells (Wight, 1970), and these probably contain little histamine (Hunt & Hunt, 1959); chopped lung from sensitized chickens does not release histamine on antigen challenge (Chand, Eyre & Deline, unpublished); H_1-receptor blockers and Compound 48/80 do not protect chickens from anaphylaxis (Pedersoli, 1973); and pulmonary vessels are relatively insensitive to histamine. They are, however, more responsive to 5-HT; large amounts of 5-HT (Meyer & Sturkie, 1974) as well as of histamine (El-Acked & Sturkie, 1972) may be released *in vivo* on antigen challenge. Thus, despite insensitivity to histamine, pulmonary vein and arterial constriction resulting in the increase in central venous pressure and consequently right heart dilatation may still occur (Lecomte & Beaumariage, 1958; Aronson *et al.*, 1961).

Nonsteroidal anti-inflammatory drugs (sodium meclofenamate, phenylbutazone), diethylcarbamazine citrate (inhibitor of SRS-A release), disodium cromoglycate, PR-D-92-EA, M & B 22948 (inhibitors of mediator release) are effective inhibitors of central venous pressor responses to antigen in chicken anaphylaxis (Chand & Eyre, unpublished). This may

support the involvement of prostaglandins and SRS-A in the reaction of pulmonary vessels to antigen.

There is considerable similarity in the symptoms of anaphylaxis and a disease causing sudden death in growing chickens commonly known as 'flips', 'lung oedema', 'flipover' or 'heart attack' (Howell, 1972; Cassidy, Gibson & Proudfoot, 1975). Histamine and other vasoactive substances may constrict pulmonary capillaries and venules resulting in increased capillary permeability and oedema formation in the lung (Somlyo & Somlyo, 1970). Sudden pulmonary venoconstriction resulting from immediate hypersensitivity reactions may be considered as one of several possible causes of this avian disease of unknown aetilogy (Carlson, personal communication).

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References

ARIENS, E.J. (1954). Affinity and intrinsic activity in the theory of competitive inhibition. I. Problems and theory. *Arch. int. Pharmacodyn. Thér.*, **99**, 32–49.

ARONSON, F.R., BILSTAD, N.M. & WOLFE, H.R. (1961). The pathology of anaphylactic shock in chickens. *Poultry Science*, **40**, 319–326.

BOLTON, T.B. & BOWMAN, W.C. (1969). Adrenoceptors in the cardiovascular system of the domestic fowl. *Eur. J. Pharmac.*, **5**, 121–131.

BURKA, J.F., DELINE, T.R., HOLROYDE, M.C. & EYRE, P. (1976). Chemical mediators of anaphylaxis (histamine, 5-Ht and SRS-A) released from horse lung and leukocytes *in vitro*. *Res. Commun. Chem. Path. & Pharmac.*, **13**, 379–388.

BURKA, J.F. & EYRE, P. (1974). Studies of prostaglandins and prostaglandin antagonists on bovine pulmonary vein *in vitro*. *Prostaglandins*, **6**, 333–343.

CASSIDY, D.M., GIBSON, M.A. & PROUDFOOT, F.G. (1975). Histology of cardiac blood clots in chicks exhibiting the "Flip-Over' syndrome. *Poultry Science*, **54**, 1882–1886.

CHAND, N. & EYRE, P. (1976). The pharmacology of anaphylaxis in the chicken intestine. *Br. J. Pharmac.*, **57**, 399–408.

CÎRSTEA, M. (1970). Discrepancies between systemic anaphylaxis and the Schultz–Dale reaction. *Int. Arch. Allergy*, **38**, 113–118.

DALE, H.H. (1913). The anaphylactic reaction of plain muscle in the guinea-pig. *J. Pharmac. exp. Thér.*, **4**, 167–223.

DALE, M.M. & OKPAKO, D.T. (1969). Recovery of anaphylactic sensitivity in the guinea-pig ileum after desensitization. *Immunology*, **17**, 653–663.

DALE, M.M. & ZILLETTI, L. (1970). The Schultz–Dale response of the longitudinal muscle strip preparation of guinea-pig ileum. *Br. J. Pharmac.*, **39**, 542–555.

EISEN, V. (1971). Plasma kinins. In *Physiology and Biochemistry of the Domestic Fowl*, Vol. 2, ed. Bell, D.J. & Freeman, B.M., pp. 973–980. London: Academic Press.

EL-ACKAD, T.M. & STURKIE, P.D. (1972). Histamine in blood and tissues of aves. *Proc. Soc. exp. Biol. Med.*, **141**, 448–451.

EYRE, P. (1970). The Schultz–Dale reaction in bovine pulmonary smooth muscles. *Br. J. Pharmac.*, **40**, 166P.

EYRE, P. (1971a). Pharmacology of pulmonary vein anaphylaxis *in vitro*. *Br. J. Pharmac.*, **43**, 302–311.

EYRE, P. (1971b). Isoprenaline stimulates α-adrenoceptors in bovine pulmonary blood vessels. *J. Pharm. Pharmac.*, **23**, 899–900.

EYRE, P. (1972). Equine pulmonary emphysema: a bronchopulmonary mould allergy. *Vet. Rec.*, **91**, 134–140.

EYRE, P. (1973). Dopamine receptors in the pulmonary vein of the calf. *Res. Commun. Chem. Path. & Pharmac.*, **5**, 27–34.

EYRE, P. (1975). Comparisons of reactivity of pulmonary vascular and airway smooth muscle of sheep and calf to tryptamine analogues, histamine and antigen. *Am. J. Vet. Res.*, **36**, 1081–1084.

EYRE, P. & DELINE, T.R. (1971a). Release of dopamine from bovine lung by specific antigen and by Compound 48/80. *Br. J. Pharmac.*, **42**, 423–427.

EYRE, P. & DELINE, T.R. (1971b). Histamine release from calf lung *in vitro* by specific antigen and by Compound 48/80. *Arch. int. Pharmacodyn. Thér.*, **192**, 347–352.

EYRE, P. & DELINE, T.R. (1972). Release of 5-hydroxytryptamine from sensitized calf lung by antigen and by Compound 48/80. *Arch. int. Pharmacodyn. Thér.*, **199**, 245–252.

FELDBERG, W. (1961). Allergische reaktions mechanismen. *Arch. Klin. exp. Derm.*, **213**, 343–381.

FURCHGOTT, R.F. & BHADRAKOM, S. (1953). Reactions of strips of rabbit aorta to epinephrine, isoproterenol, sodium nitrite and other drugs. *J. Pharmac. exp. Ther.*, **108**, 129–143.

HILLER, K. & KARIM, S.M.M. (1968). Effects of prostaglandins E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$ on isolated human umbilical and placental blood vessels. *J. Obstet. Gynaecol. Br. Cwlth.*, **75**, 667–673.

HOLROYDE, M.C. & EYRE, P. (1975). Reactivity of isolated bovine mesenteric and hepatic veins to vasoactive agents and specific antigen. *Eur. J. Pharmac.*, **30**, 36–42.

HOWELL, J. (1972). 'Flip over' disease. *25th Meeting of the Can. Poultry Dis. Conference*, May 31–June 1, Animal Diseases Research Institute, Hull, Quebec.

HUNT, T.E. & HUNT, E.A. (1959. Blood basophils of cockerels before and after intravenous injection of Compound 48/80. *Anat. Rec.*, **133**, 19–33.

JOINER, P.D., KADOWITZ, P.J., HUGHES, J.P. & HYMAN, A.L. (1975). Actions of prostaglandins E_1 and $F_{2\alpha}$ on isolated intrapulmonary vascular smooth muscle. *Proc. Soc. exp. biol. Med.*, **150**, 414–421.

KELLAWAY, C.H. (1930). The anaphylactic reaction of the

isolated uterus of the rat. *Br. J. exp. Path.*, **11**, 72–80.

LECOMTE, P.J. (1958. Réactions anaphylactiques *in vitro* des artères pulmonaires du lapin. *Int. Arch. Allergy*, **12**, 339–346.

LECOMTE, J. & BEAUMARIAGE, M.L. (1958). Le choc anaphylactique du coq. Rôle de l'histamine dans son déterminisme. *Int. Arch. Allergy*, **13**, 145–180.

LEWIS, A.J. & EYRE, P. (1972). Some cardiovascular and respitatory effects of prostaglandins E_1, E_2 and $F_{2\alpha}$ in the calf. *Prostaglandins*, **2**, 55–64.

MEYER, D.C. & STURKIE, P.D. (1974). Distribution of serotonin among blood cells of the domestic fowl. *Proc. Soc. exp. Biol. Med.*, **147**, 382–391.

OKPAKO, D.T. (1970). Antigen-dose response relationships in guinea-pig ileum anaphylaxis. *Int. Arch. Allergy*, **38**, 474–481.

PEDERSOLI, W.M. (1973). Effects of acute anaphylactic shock on arterial blood pressure of anaesthetized chicken. *Am. J. Vet. Res.*, **34**, 881–885.

SCHILD, H.O. (1956). Histamine release and anaphylaxis. In *Histamine*, Ciba Foundation Symposium, ed. Wolstenholme, G.E.W. & O'Connor, C.M., pp. 139–149. Boston: Little, Brown & Company.

SCHILD, H.O., HAWKINS, D.F., MONGAR, J.L. & HERXHEIMER, H. (1951). Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen. Histamine release and muscular contraction. *Lancet*, **ii**, 376–382.

SCHULTZ, W.H. (1910). Physiological studies in anaphylaxis. I. The reaction of smooth muscle of the guinea pig sensitized with horse serum. *J. Pharmac. exp. Ther.*, **1**, 549–567.

SOMLYO, A.P. & SOMLYO, A.V. (1970). Vascular smooth muscle. II. Pharmacology of normal and hypertensive vessels. *Pharmac. Rev.*, **22**, 249–353.

SOMLYO, A.P., SOMLYO, A.V. & WOO, C.Y. (1967). Neurohypophysial peptide interaction with magnesium in avian vascular smooth muscle. *J. Physiol. Lond.*, **192**, 657–668.

SÖRENBY, L. (1975). Inhibition of antigen-induced tone in isolated trachea. *Eur. J. Pharmac.*, **31**, 374–376.

STRONG, C.G. & BOHR, D.F. (1967). Effects of prostaglandins E_1, E_2, A_1 and $F_{1\alpha}$ on isolated vascular smooth muscle. *Am. J. Physiol.*, **213**, 725–733.

WIGHT, P.A.L. (1970). The mast cells of Gallus domesticus. I. Distribution and ultrastructure. *Acta Anat.*, **75**, 100–113.

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