Short communications

Histamine H_2-receptors modulate systemic anaphylaxis: a dual cardiovascular action of histamine in calves

P. EYRE AND P. W. WELLS*

Pharmacology Laboratory, Department of Biomedical Sciences, University of Guelph, Guelph, Ontario, Canada

Depressor changes in carotid blood pressure caused by histamine or anaphylaxis in calves, were incompletely blocked by the H_1-receptor antagonist mepyramine. Burimamide, the selective histamine H_2-receptor antagonist, potentiated the depressor actions of histamine and anaphylaxis. Potentiated depressor responses were inhibited by mepyramine. Observations are consistent with histamine stimulating both H_1- and H_2-receptors to cause respectively vasodilatation and vasoconstriction.

Mepyramine has been classified as a histamine-H_1-receptor antagonist (Ash & Schild, 1966) and it is recognized that this agent does not antagonize all the actions of histamine. Mepyramine does not inhibit the effect of histamine on gastric secretion (Ashford, Heller & Smart, 1949), rat uterus (Dutta, 1949) sheep bronchus (Eyre, 1969), cat trachea (Maengwyn-Davies, 1968) and a component of cat blood pressure (Black, Duncan, Durant, Ganellin & Parsons, 1972). Mepyramine-resistant histamine receptors are defined as H_2-receptors (Black *et al.*, 1972). A new agent, burimamide, antagonizes H_2-receptor-mediated effects of histamine on gastric secretion (Black *et al.*, 1972; Wyllie, Hesselbo & Black, 1972), sheep bronchial and cat tracheal relaxations (Eyre, 1973) and cat blood pressure (Black *et al.*, 1972).

Despite the reported elevation of histamine concentration in the plasma of calves during anaphylactic shock (Eyre, Lewis & Wells, 1973), mepyramine does not effectively control anaphylaxis in this species; whereas sodium meclofenamate and diethylcarbamazine (which are known to antagonize kinins, slow reacting substance-A and prostaglandins) do so almost completely (Wells & Eyre, 1972; Eyre *et al.*, 1973; Wells, Eyre & Lumsden, 1973). This suggested to us that kinins and pharmacologically-active lipids might be of greater significance in bovine anaphylaxis than the amines, histamine or 5-hydroxytryptamine. Another explanation for the low anti-anaphylactic potency of mepyramine in calves appeared possible however. It seemed feasible that histamine H_2-receptors might play a role in bovine anaphylactic shock. Thus the present study was undertaken to determine the effects of burimamide on mepyramine-resistant systemic depressor responses to histamine and anaphylaxis in calves.

Methods.—Twenty male Jersey and Guernsey calves one to two months of age, weighing 30–70 kg were sensitized with whole horse serum and Freund's complete adjuvant (Eyre & Lewis, 1972; Eyre, Lewis & Wells, 1973). Blood pressures were measured in the common carotid and pulmonary artery under pentobarbitone anaesthesia as previously described (Lewis & Eyre, 1972; Eyre, *et al.*, 1973; Wells, *et al.*, 1973). All drug administrations were made into a cannulated tarsal vein.

Animals were divided into four groups of four and two groups of two. In group 1, after an 'equilibration' period of approximately 15 min, histamine, 5-hydroxytryptamine and acetyl β-methyl choline (methacholine) were administered randomly at several dose levels in four calves in order to establish three-point dose-response curves for each agonist. Horse serum (0·2 ml kg^{-1}) was then administered intravenously to induce anaphylaxis.

The four calves of group 2 were similarly treated except that dose-response curves for histamine, 5-hydroxytryptamine and methacholine were re-established 15 min after administration of mepyramine maleate, 5×5^{-6} mol kg^{-1} as a single injection. The effectivenescs of mepyramine was estimated by measuring the dose-ratio of each agonist: i.e. the ratio of doses of agonist giving equal carotid depressor responses in the presence and absence of antagonist (Gaddum, Hameed, Hathway & Stephens, 1955). Anaphylaxis was then

* Present address: Animal Diseases Research Association, Moredun Institute, Edinburgh EH17 7JH, Scotland.

induced with horse serum in each calf as before.

Group 3 consisted of two calves identically treated to group 2 except that the dose of mepyramine was increased to $2{\cdot}5\times10^{-5}$ mol kg^{-1}.

In group 4, following the establishment of agonist dose-response curves, four calves received burimamide (3×10^{-7} mol kg^{-1} min^{-1}) continuously to the end of the experiment. Agonists were re-tested and dose-response curves re-established prior to challenge with antigen after 30 minutes.

Group 5 consisted of two calves identically treated to group 4 except that the dose of burimamide was increased to 5×10^{-6} mol kg^{-1} min^{-1}.

In the four calves of group 6, agonists were tested before and after administration of burimamide (3×10^{-7} mol kg^{-1} min^{-1}) continuously as in group 4. However, after 20 min of burimamide infusion, mepyramine (5×10^{-6} mol kg^{-1}) was administered as a single injection. After a further 10–15 min, agonist dose-ratios were established and anaphylaxis induced.

Results. — As previously reported, histamine and 5-hydroxytryptamine caused carotid depressor responses (Lewis & Eyre, 1972; Eyre *et al.*, 1973). Metha-

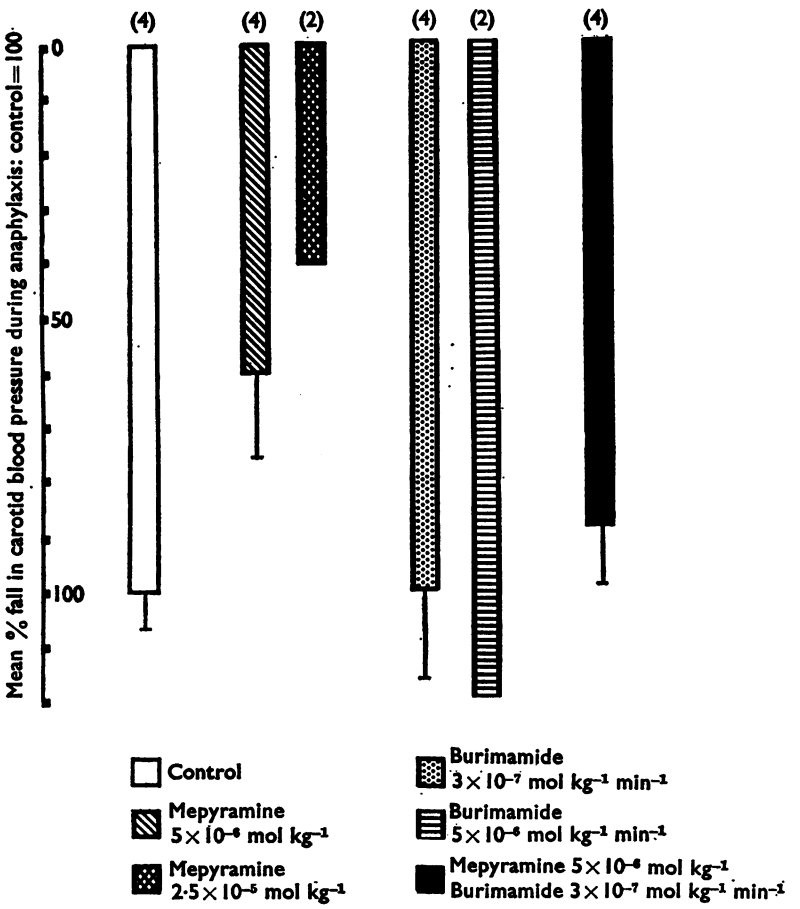

FIG. 1. Mean percentage decrease in femoral arterial blood pressure (±S.D.) in six groups of calves subjected to acute systemic anaphylactic shock under pentobarbitone anaesthesia. Group 1, the open column, represents control anaphylactic shock equivalent to −90 mmHg, (mean arterial pressure) converted to 100%. Prior to induction of anaphylaxis, mepyramine was administered to groups 2 and 3, burimamide to groups 4 and 5, and mepyramine and burimamide combined to group 6. Numbers in parentheses on columns refer to numbers of observations.

choline (>0·05 μg kg^{-1}) consistently reduced systemic blood pressure. Anaphylaxis in the control group was characterized by systemic arterial depression representing a change in mean arterial pressure of −90 mmHg (−64%: $n=4$). After injection of mepyramine (5×10^{-6} mol kg^{-1}), the dose-response curve to histamine was displaced to the right (mean dose-ratio=26: $n=4$), whereas the effects of 5-hydroxytryptamine and methacholine were unchanged. In the same calves, systemic anaphylactic shock, measured in terms of mean carotid blood pressure, was suppressed 40% ($n=4$) (Figure 1). The five-fold increase in mepyramine dosage to group 3 blocked anaphylaxis 60% ($n=2$), and increased the histamine dose-ratio to 100 ($n=2$).

In contrast, burimamide (3×10^{-7} mol kg^{-1} min^{-1}) clearly potentiated the depressor response to histamine (dose-ratio=0·55: $n=4$) without displacing the dose-response curves to 5-hydroxytryptamine or methacholine. Anaphylactic shock induced in the presence of burimamide was identical to that in the control group. Increasing the concentration of burimamide to 5×10^{-6} mol kg^{-1} min^{-1} further potentiated histamine depressor responses (dose-ratio 0·35: $n=2$) and furthermore intensified anaphylactic shock by 20% ($n=2$).

The potentiating action of burimamide was antagonized completely by mepyramine (Figure 1).

Discussion.—Present findings are consistent with a dual histamine receptor mechanism in peripheral blood vessels of calves. It seems possible that systemic depressor responses to histamine in the calf may represent an algebraic sum of two components (1) a mepyramine-sensitive depressor effect, presumably mediated by H_1-receptors; (2) a mepyramine-resistant, burimamide-sensitive anti-depressor effect, evidently mediated by H_2 receptors. The full extent of the depressor component was revealed by burimamide, particularly in group 5 at the dose rate of burimamide 5×10^{-6} mol kg^{-1} min^{-1}. However, large doses of mepyramine ($2{\cdot}5\times10^{-5}$ mol kg^{-1}) failed to 'unmask' any actual pressor effect of histamine. Indeed, this concentration of mepyramine failed to block all the participating 'depressant' H_1-receptors, which may thus have continued to neutralize any postulated H_2-pressor component. It was not possible to examine the effects of greater doses of mepyramine owing to toxic manifestations of the drug.

Responses of calves to histamine differ from those of cats. Black *et al.* (1972) described H_1- and H_2-receptors, both acting in the same direction to lower blood pressure in the cat. Hence in that species, mepyramine and burimamide reinforce each other in the blockade of histamine depressor responses. In the calf it appears that the H_2-receptors modulate the depressor effects of H_1-receptor stimulation. Preliminary studies of H_2-receptor distribution in ruminants have revealed that histamine-induced vasoconstrictions of calf pulmonary vasculature were potentiated by burimamide, and these could be blocked by mepyramine. This suggests a wider distribution of both types of histamine receptors.

It is not unreasonable to presume that tissue histamine released endogenously by antigen/antibody interaction would stimulate both classes of histamine receptors in the same way as exogenously injected histamine. Bearing in mind that anaphylaxis involves many chemical mediators in addition to histamine, it is possible to suggest that part of the action of histamine liberated in anaphylaxis in calves serves to *modulate* the overall systemic depressor response. The failure of mepyramine to antagonize anaphylactic hypotension in calves probably is not due to the activation of H_2-receptors. It does not seem likely that burimamide will be of value in controlling diseases of cattle which involve anaphylactic hypersensitivity.

We are indebted to Professor H. G. Downie for his continued support and encouragement and to Mr. T. R. Deline for invaluable technical assistance. We gratefully acknowledge generous gifts of drugs: mepyramine maleate from Dr. F. Poulin of Poulenc Ltd., Montréal, Canada, and burimamide from Dr. J. W. Black of Smith, Kline & French Ltd., Welwyn Garden City, England. The work was supported in part by the Ontario Ministry of Agriculture and Food and also by grant A5937 of the National Research Council of Canada.

REFERENCES

ASH, A. S. F. & SCHILD, H. O. (1966). Receptors mediating some actions of histamine. *Br. J. Pharmac. Chemother.*, **27**, 427–439.

ASHFORD, C. A., HELLER, H. & SMART, G. A. (1949). The effects of antihistamine substances on gastric secretion. *Br. J. Pharmac. Chemother.*, **4**, 153–161.

BLACK, J. W., DUNCAN, W. A. M., DURANT, C. J., GANELLIN, C. R. & PARSONS, E. M. (1972). Definition and antagonism of histamine H_2-receptors. *Nature*, (*Lond.*), **236**, 385–390.

DUTTA, N. K. (1949). Some pharmacological properties common to antihistamine compounds. *Br. J. Pharmac. Chemother.*, **4**, 281–289.

EYRE, P. (1969). The pharmacology of sheep tracheobronchial muscle—a relaxant effect of histamine on isolated bronchi. *Br' J. Pharmac.*, **36**, 409–417.

EYRE, P. (1973). Histamine H_2-receptors in sheep bronchus and cat trachea: the action of burimamide. *Br. J. Pharmac.*, **48**, 321-323.

EYRE, P. & LEWIS, A. J. (1972). Production of kinins in bovine anaphylactic shock. *Br. J. Pharmac.*, **44**, 311–313.

EYRE, P., LEWIS, A. J. & WELLS, P. W. (1973). Acute systemic anaphylaxis in the calf. *Br. J. Pharmac.*, **47**, 504-516.

GADDUM, J. H., HAMEED, K. A., HATHWAY, D. E. & STEPHENS, F. F. (1955). Quantitative studies of antagonists for 5-hydroxytryptamine. *Q. Jl. exp. Physiol.* **40**, 49–74.

LEWIS, A. J. & EYRE, P. (1972). Some cardiorespiratory effects of histamine, 5-hydroxytryptamine and compound 48/80 in the calf. *Can. J. Physiol. Pharmac.*, **50**, 545–553.

MAENGWYN-DAVIES, G. D. (1968). The dual mode of action of histamine in the cat isolated tracheal chain. *J. Pharm. Pharmac.*, **20**, 572–573.

WELLS, P. W. & EYRE, P. (1972). The pharmacology of passive cutaneous anaphylaxis in the calf. *Can. J. Physiol. Pharmac.*, **50**, 255–263.

WELLS, P. W., EYRE, P. & LUMSDEN, J. H. (1973). Hematological and pathological changes in acute systemic anaphylaxis in calves—effects of pharmacological agents. *Can. J. Comp. Med.*, **37**, 119-129.

WYLLIE, J. H., HESSELBO, T. & BLACK, J. W. (1972). Effects in man of histamine H_2-receptor blockade by burimamide. *Lancet*, **2**, 1117–1120.

(*Received April* 16, 1973)