Short communications

Some effects of burimamide on the isolated perfused pulmonary circulation of the guinea-pig

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Infusions of burimamide were found to potentiate the pressor response to histamine and abolish the depressor response to histamine in the presence of mepyramine, in the isolated perfused guinea-pig pulmonary circulation. It is concluded that the depressor response to histamine is due to stimulation of histamine H_2-receptors in the pulmonary vessels.

Okpako (1972a, b) has described a pressor action of histamine on guinea-pig pulmonary vessels which was converted to a depressor response in the presence of mepyramine. In the course of studies on anaphylaxis in guinea-pig lung, it was noted that, although histamine was released (Bartosch, Feldberg & Nagel, 1932), mepyramine gave only a partial protection against anaphylactic bronchoconstriction (Smith, 1961; Goadby & Smith, 1964). The existence of a mepyramine-resistant effect of histamine in guinea-pig lung was thus considered of great interest.

Ash & Schild (1966) suggested that histamine interacted with two types of receptors: those effects selectively antagonized by mepyramine were mediated by H_1-receptors, whereas the mepyramine-resistant effects resulted from stimulation of H_2-receptors. Burimamide has been recently introduced as a selective histamine H_2-receptor antagonist (Black, Durant, Duncan, Ganellin & Parsons, 1972) and therefore the possibility that it could be used to block the mepyramine-resistant effects of histamine in guinea-pig lung was investigated.

Methods.—The heart and lungs were quickly excised from freshly killed guinea-pigs of either sex, weighing 400 to 600 g, and the pulmonary artery was cannulated via an incision in the right ventricle. An incision was made in the left ventricle and the auricles were removed. The lungs were suspended, via a tracheal cannula, in a constant temperature chamber. The pulmonary vessels were perfused with Krebs solution containing (mM) NaCl 119·0, KCl 4·7, $CaCl_2$ 2·5, MgCl 1·2, $NaHCO_3$ 25·0, NaH_2PO_4 1·2 and glucose 11·5. The solution was equilibrated with oxygen containing 5% CO_2 at 37° C and a perfusion rate of 5 ml/min was maintained with a Watson-Marlow Constant Flow Inducer (MRHE 200). The changes in perfusion pressure were recorded by means of a Bell & Howell pressure transducer (4-327-L 221), connected immediately in front of the pulmonary cannula. The output of the transducer was displayed on a Devices M2 recorder. The pressure changes were also monitored by a water manometer connected in parallel with the transducer. Drugs were either injected into the pulmonary arterial cannula in a constant

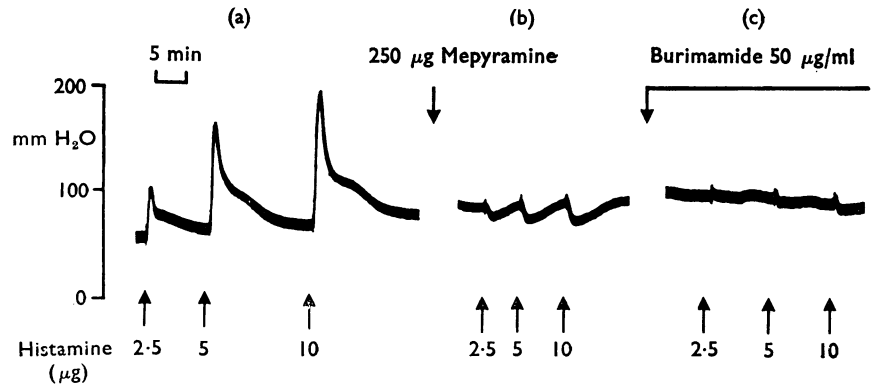

FIG. 1. Effect of histamine on the perfused pulmonary circulation of the guinea-pig. (a) Perfused with Krebs Ringer solution (5 ml/min) at 37° C. (b) 30 min after injection of 250 μg mepyramine maleate. (c) perfused with 50 μg/ml burimamide in Krebs solution.

volume of 0·1 ml of Krebs solution or infused in the perfusion fluid at a rate of 5 ml/minute.

Results.—Histamine produced dose-related increases in perfusion pressure (Fig. 1a) in six lungs, ranging from 45·75 ± 6·02 (Mean ± S.E.M.) mmH_2O in response to an injected dose of $2{\cdot}27 \times 10^{-8}$ mol to 86·37 ± 8·88 mmH_2O after a dose of $9{\cdot}09 \times 10^{-8}$ mol. Doses above $9{\cdot}09 \times 10^{-8}$ mol did not produce any further increase in response.

The injection of $6{\cdot}25 \times 10^{-7}$ mol mepyramine maleate into the pulmonary circulation converted the increases in perfusion pressure following injection of histamine into decreases (Figure 1b). The comparable responses to those above were −10·16 ± 1·29 mmH_2O at a dose of $2{\cdot}27 \times 10^{-8}$ mol histamine and −11·89 ± 0·57 mmH_2O at a dose of $9{\cdot}09 \times 10^{-8}$ mol. In some preparations mepyramine caused a small increase in pressure during the 30 min following injection.

Infusion of burimamide ($2{\cdot}5 \times 10^{-4}$M) in Krebs solution potentiated the increase in perfusion pressure due to histamine and abolished, or converted to a slight rise, the decreases in perfusion pressure seen after pretreatment with mepyramine (Figure 1c).

Decreases in perfusion pressure in response to injections of isoprenaline ($0{\cdot}25 \times 10^{-9}$ mol to 1×10^{-9} mol) were not abolished by infusions of burimamide ($2{\cdot}5 \times 10^{-4}$M) either alone or following an injection of mepyramine.

Discussion.—These results confirm the findings of Okpako (1972a, b) that histamine in the presence of mepyramine produces vasodilator responses in perfused guinea-pig pulmonary vessels. These depressor responses were blocked by an infusion of burimamide, and would thus appear to be mediated by histamine H_2-receptors. Stimulation of H_2-receptors would seem to form part of the normal response of guinea-pig pulmonary vessels to histamine, since the pressor response was greater in the presence of burimamide. The selectivity of burimamide was shown by its failure to antagonize the depressor response to isoprenaline.

Burimamide thus provides a means of distinguishing between the effects of histamine H_2-receptor stimulation and other mepyramine-resistant responses due to substances such as prostaglandins and slow reacting substance (SRS-A) which are also released during an aphylaxis in guinea-pig lung (Piper & Vane, 1969).

The burimamide used was a generous gift from Dr. J. W. Black, Smith, Kline & French Research Laboratories, Welwyn Garden City. Mepyramine maleate was supplied by May & Baker Ltd., Dagenham.

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(*Received May* 4, 1973)