Effect of phospholipids on histamine release

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Goth & Adams (1970) have shown that phosphatidyl serine has a selective effect on histamine release by dextran or ovomucoid from rat peritoneal cells. We have found that certain phospholipids interact with rat mast cells to produce an enhanced anaphylactic secretion of histamine. This potentiation was produced by acidic phospholipids, phosphatidyl serine (PS) and inositol (PI) which gave graded effects over the dose range 1–10 μg/ml. The neutral phospholipids, phosphatidyl ethanolamine and choline were inactive.

The degree of potentiation depended on the type of mast cell. It was greatest with rat isolated peritoneal cells (2–5 fold increase). Histamine release from mesentery and lung was less affected (about 1·6 and 1·3 fold increase respectively).

The anaphylactic release of histamine from peritoneal mast cells requires the presence of calcium ions. The optimal calcium concentration in the absence of added phospholipid was found to be about 1 mM. When PS was added (100 μg/ml) the release was potentiated but a further increase was obtained by raising the calcium concentration to 10 mM. The two acidic phospholipids which have been found to potentiate histamine release are known to bind calcium ions (Hauser & Dawson, 1967), whilst the neutral phospholipids neither potentiate histamine release nor bind calcium. An interaction of phospholipids with calcium may be involved in the anaphylactic secretion of histamine.

The enhancing effect of acidic phospholipids does not extend to histamine release by compound 48/80. On the contrary, release by this agent is inhibited by both PS and PI. In the presence of PS (100 μg/ml) the log-dose response curve for 48/80 shows a parallel shift of 0·3 log units. Similar inhibitory effects have been obtained in the three preparations studied: isolated peritoneal cells, chopped mesentery and chopped lung tissue. These findings point to important differences in the mode of action of antigen and 48/80.

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Resistance of rats to carrageenan and to adjuvant-induced arthritis

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Production of an inflammatory oedema in the rat paw by injected carrageenan has been widely adopted as an experimental model for the evaluation of potential anti-inflammatory drugs, particularly as their relative activities in this test correlate well with their anti-inflammatory activities in man. Recently, Willis (1969) and Di Rosa & Willoughby (1971) reported that this oedema is mediated by histamine and 5-hydroxytryptamine (5-HT) during the first hour, after which the increased vascular

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permeability is maintained by kinin release up to 2·5 h and then by prostaglandin release up to 6 hours. Mononuclear leucocyte migration into the inflamed site occurs during this latter phase.

Whilst testing different strains of rat for their reactivity to carrageenan, we found that Wistar rats, genetically resistant to the anaphylactoid reaction produced by dextran, failed to react to carrageenan (0·1 ml of 1%), injected into the subplantar aspect of one hind paw, until 1 h after injection after which the oedema increased to reach, by 6 h, almost the value obtained using Wistar rats sensitive to dextran. On the other hand, these sensitive rats always showed a marked reaction to 1 mg of carrageenan by 30 minutes. The resistant animals contain comparable amounts of histamine and 5-HT but release only relatively small quantities when injected with dextran (Harris & West, 1963), and form and release kinins only with difficulty when subjected to different forms of shock (Starr & West, 1970). Hence, their prostaglandin release by carrageenan appears to be unimpaired and they yield a result which closely follows that of Di Rosa & Willoughby (1971) who used rats sensitive to dextran but depleted of their stores of histamine, 5-HT and kinin before injecting carrageenan.

The intradermal injection of complete Freund's adjuvant into one hind paw of a rat results in disseminated inflammatory lesions of joints and skin after a latent period of about 14 days, a condition which resembles human rheumatoid arthritis in many respects. In 1969 Pelczarska reported that this adjuvant-induced arthritis was inhibited by treating the animals with hypostamine, an inhibitor of histidine decarboxylase. However, daily doses of 50 mg/kg intraperitoneally of NSD-1034 (N-(3-hydroxybenzyl)-N-methylhydrazine dihydrogen phosphate), another potent inhibitor of histidine decarboxylase, failed to modify the course of the reaction which therefore appears not to involve histamine. In contrast, Wistar rats resistant to dextran did not develop the arthritis, even without inhibitor; the secondary symptoms of the cell-mediated inflammation did not show at any time.

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Prostaglandin generation maintains the smooth muscle tone of the rabbit isolated jejunum

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Prostaglandin (PG) synthesis and release *in vitro* or *in vivo* is blocked by non-steroidal anti-inflammatory drugs (Vane, 1971; Ferreira, Moncada & Vane, 1971; Smith & Willis, 1971; Aiken & Vane, 1971). We have now studied the action of a