Calcium and the inhibition of histamine release from rat peritoneal mast cells by non-steroid anti-inflammatory agents

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Non-steroid anti-inflammatory drugs inhibit the release of histamine from rat peritoneal mast cells induced by a variety of stimulants including antigen and compound 48/80 (Thomas & Whittle, 1976). Although these effects could result from an elevation of mast cell cyclic AMP levels via phosphodiesterase inhibition, histamine release stimulated by the calcium ionophore (A23187) was also inhibited, suggesting that other inhibitory mechanisms may also operate; an increase in cyclic AMP levels is not thought to prevent ionophore-induced histamine release (Garland & Mongar, 1976). In the present study, the possibilities that non-steroid anti-inflammatory drugs affect the mobilization of calcium ions, or the processes of oxidative metabolism involved in histamine release, have been investigated.

Mast cells were obtained by lavage of the rat peritoneal cavity with a modified buffered medium (pH 7) and the histamine release following incubation was determined by fluorometric assay. Submaximal histamine release (50–70% of the total histamine content of the mast cells), induced by compound 48/80 (0.15–0.3 μg/ml) or ionophore-A23187 (0.25–0.5 μg/ml) was inhibited by 2, 4 dinitrophenol (50–100 μg/ml) which uncouples oxidative phosphorylation, and by antimycin-A (0.02–0.5 μg/ml) which acts on the cytochrome system. This inhibition was prevented by preincubation with glucose (1–5 mM)-containing medium (10 experiments), as shown by others (see Diamant, 1975). In contrast, the inhibition of histamine release by indomethacin (10–80 μg/ml) or sodium meclofenamate (0.5–10 μg/ml) was not significantly altered by glucose (1–5 mM)-incubation (8 experiments).

Histamine release induced by the ionophore-A23187 was dependent on the dose (0.1–0.5 μg/ml) and on the calcium concentration of the incubation medium. Optimal histamine release, with a submaximal dose of the ionophore (0.33 μg/ml), was obtained with a calcium concentration of 0.75 mM; an increase in the calcium concentration up to 3 mM did not elevate the release further. The dose-dependent inhibition by indomethacin (10–40 μg/ml) or meclofenamate (1–5 μg/ml) of histamine release stimulated by this ionophore was related to the calcium concentration of the incubation medium. In four experiments, the marked inhibition of ionophore (0.33 μg/ml)-induced release by meclofenamate (5 μg/ml) was significantly reduced (from $81.4 \pm 2.9\%$ to $7.6 \pm 3.9\%$, mean ± s.e. mean; $P < 0.001$) when the calcium concentration was increased from 0.75 mM to 3 mM. In contrast, the inhibition of ionophore (0.33 μg/ml)-induced release by antimycin-A was not reversed by an increase in the calcium concentration (5 experiments).

These results show that whereas the inhibition of histamine release from rat mast cells, by drugs known to interfere with energy production from oxidative metabolism, can be reversed by incubation with glucose (by promoting anaerobic glycolysis), glucose-incubation did not prevent the inhibition of release produced by indomethacin or meclofenamate. The observation that an increase in the calcium concentration abolished the inhibition of ionophore-stimulated release suggests an action on a calcium-dependent stage in the release process. It has been shown that several aspirin-like drugs can interfere with the uptake and binding of calcium in various tissues (Northover, 1973). Thus, the inhibition of histamine release by non-steroid anti-inflammatory drugs could reflect actions on calcium influx into the mast cell, or on calcium mobilization or utilization within the mast cell.

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