

Histamine release from mast cells by polyamines: an NMDA receptor-mediated event?

WENDY M. PURCELL, KAREN M. DOYLE, LOVEENA BAGGA and MARIANKA DERKS

CellTox Centre, Division of Biosciences, University of Hertfordshire, Hatfield, Herts. AL10 9AB, U.K.

In recent years it has become apparent that the role of the mast cell is not confined to immediate hypersensitivity reactions and that the cell may participate in a range of non-IgE mediated processes. The natural polyamines induce histamine release from rat peritoneal mast cells (RPMC) in a concentration- and energy-dependent process with a rank order of potency of spermine > spermidine > putrescine [1]; compound 48/80, a synthetic polyamine, is regarded as a classic mast cell secretagogue [1]. However, the mechanism by which these agents trigger secretion in this system remains to be elucidated. It has been variously suggested that they interact with mast cells via direct stimulation of G-proteins [1] or with ill-defined polyamine 'receptors' [2]. We have explored the possibility that spermine triggers histamine release from RPMC via interaction with a polyamine site associated with the NMDA receptor complex.

In the present study RPMC, collected by peritoneal lavage [3], were incubated (37°C, 15 min) with either spermine (10^{-5} - 3×10^{-3} M) or compound 48/80 (C48/80: 0.01-100 µg/ml) and the presence of histamine in the cell supernatant determined using the OPT-condensate fluorimetric assay [3]. The effect of arcaine, ifenprodil and MK801 alone was determined and their effect on agonist-induced histamine output assessed; compounds were added at the same time as the agonist.

Spermine induced histamine secretion from RPMC in a concentration dependent manner, with an EC₅₀ of 3×10^{-4} M and maximal release of $53.9 \pm 10.8\%$ of total histamine at a concentration of 10^{-3} M spermine. C48/80 had an EC₅₀ of 0.1 µg/ml and induced maximal histamine release of $82.5 \pm 3.7\%$ at a concentration of 30 µg/ml.

Arcaine has been proposed to act as a competitive inhibitor at the polyamine site on the NMDA receptor macrocomplex [4]. Arcaine was observed to exhibit the characteristics of a partial agonist in this system in that concentrations of 10^{-6} - 3×10^{-4} M had no significant effect on RPMC, while at 10^{-3} M arcaine induced histamine release ($26.6 \pm 1.4\%$). Arcaine (10^{-4} M) inhibited spermine-induced histamine release from RPMC (Figure 1).

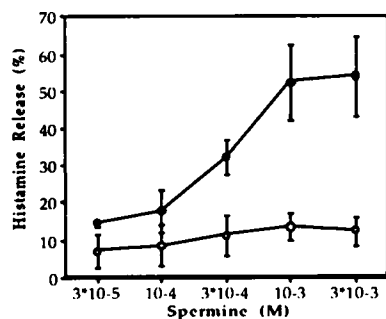


Figure 1

Effect of arcaine (10^{-4} M; open symbols) on spermine-induced (closed symbols) histamine release from rat peritoneal mast cells. Results are mean \pm SEM, n=6.

Ifenprodil (10^{-6} - 10^{-3} M), an NMDA receptor antagonist [5] and MK801 (10^{-6} - 10^{-3} M), an open-channel blocker [6], had no effect alone on histamine release from RPMC. Both ifenprodil and MK801 inhibited spermine- (3×10^{-4} M) and C48/80- (0.1 µg/ml) induced histamine secretion in a concentration dependent manner (Figure 2). The percentage inhibition was more pronounced against spermine than compound 48/80. Ifenprodil and MK801 (10^{-3} M) inhibited spermine-induced histamine release ($33.7 \pm 1.5\%$ at 3×10^{-4} M) by 89% and 70% respectively; this compares with inhibition of compound 48/80-induced histamine output ($44.5 \pm 2.9\%$ at 0.1 µg/ml) of 21% and 48% respectively.

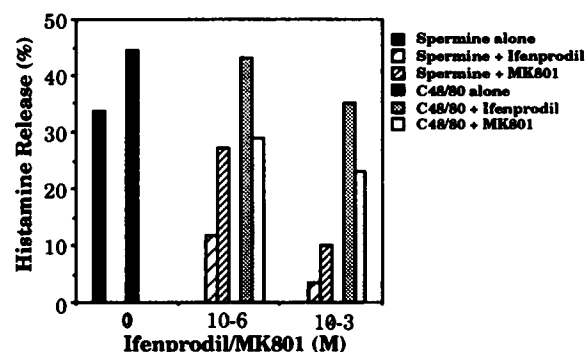


Figure 2

Effect of Ifenprodil and MK801 on spermine- (3×10^{-4} M) and compound 48/80- (0.1 µg/ml) induced histamine release from RPMC. Results are mean values, n=6.

The natural polyamine spermine and the synthetic polyamine compound C48/80 induce histamine release from RPMC in a concentration dependent manner. It is known that intraperitoneal injection of spermine to rats increases the histamine content of the blood by a factor of two [7]: this may reflect release of histamine from peritoneal mast cells. Arcaine, ifenprodil and MK801 act as antagonists of histamine secretion induced from RPMC by these agents. It is clear that ifenprodil and MK801 are more potent inhibitors of spermine-induced histamine release than C48/80-triggered histamine secretion; C48/80 may interact with peritoneal mast cells by a mechanism distinct from the polyamine receptor site. Taken together this data would support the hypothesis that spermine induces histamine release from RPMC by interaction with a polyamine site on an NMDA receptor macrocomplex. Whether this site is distinct from that described in brain tissue [6] remains to be elucidated, since neither glutamate nor glycine were added to the mast cells.

- [1] Bueb, J.L., Mousli, M. & Landry, Y. (1991) Agents & Actions **33**, 84-86
- [2] Read, G.W., Hong, S.M. & Kiefer, F. (1982) J. Pharm. Exp. Ther. **222**, 652-657
- [3] Purcell, W.M., Cohen, D.L. & Hanahoe, T.H.P. (1989) Int. Archs. Allergy Appl. Immunol. **90**, 382-386
- [4] Reynolds, I.J. (1990) Eup. J. Pharm. **177**, 215-216
- [5] Graham, D., Darles, G. & Langer, S.Z. (1992) Eup. J. Pharm. **226**, 373-376
- [6] Williams, K., Romano, C., Dichter, M.A. & Molinoff, P.B. (1991) Life Sci. **48**, 469-498.
- [7] Shaw, G.G. (1977) Biochem. Pharm. **26**, 1450-1451