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Does the mast cell have an intrinsic role in the pathogenesis of interstitial cystitis?

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Abstract. In order to examine the role of mast cells in the inflammatory bladder disease interstitial cystitis, mast cells isolated from the human bladder of normal and diseased tissue were challenged with a range of secretagogues. Calcium ionophore A23187 and anti-IgE caused histamine release from all bladder mast cells in a dose-related manner. Mast cells from the diseased tissue were far more responsive than those from the normal tissue. Mast cells from the muscle of normal bladder were responsive towards substance P and compound 48/80. However, mast cells from interstitial cystitis bladder did not release significant amounts of histamine with these two secretagogues.

Interstitial cystitis (IC) is a chronic inflammatory disorder of the urinary bladder and affects mainly middle-aged females. There is no agreement as to the cause of IC, but it has been associated with a significant increase in mast cell numbers within the detrusor muscle of the bladder [1–3]. To examine further the role of the mast cell in IC, we have isolated and functionally compared IC bladder mast cells with those from macroscopically normal tissue of carcinoma patients.

Materials and methods

The mucosa and muscle of human bladder samples were separated by blunt dissection and chopped mechanically followed by digestion with the enzyme collagenase (Sigma) [4]. The resulting cell suspension was then washed three times in full HEPES-buffered Tyrode's solution (FHB) supplemented with 1 mg/ml bovine serum albumin (BDH Chemicals). In the histamine release experiments [5], the mast cells were challenged with either anti-human IgE (Dako), ionophore A23187 (Calbiochem), substance P (Peninsula) or compound 48/80 (Sigma) for 10 min. The reaction was terminated by the addition of ice-cold FHB followed by centrifugation. The supernatant was separated from the cell pellet and both assayed for histamine. Histamine was measured using an automated spectrofluorometric assay. Values for histamine release are expressed as a percentage of the total cellular histamine. All values are corrected for the spontaneous release of histamine in the absence of any stimuli.

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All values are given as means ± SEM for the number of observations (n) noted.

Results

All cells were found to be highly viable (>90%) as judged by the Trypan blue exclusion test and the uniformly low spontaneous histamine release (<7.0%). The immunological ligand, anti-human IgE, produced a dose-dependent release of histamine from all bladder mast cells (Table 1). The striking feature, however, is that mast cells isolated from the IC bladder tissue were far more responsive than those isolated from the normal tissue. Maximal histamine release at an anti-IgE dilution of 1/100 was found to be 28% and 26% for muscle and mucosa, respectively, of the diseased tissue, whilst the release from mast cells isolated from the normal tissue did not exceed 8%. Ionophore A23187 also induced histamine release in a dose-related manner. Again, the mast cells from the diseased tissue were shown to be more responsive than those from the normal tissue. Maximal histamine releases at ionophore concentrations of 0.5–1.0 μM were 68% for IC muscle, 51% for IC mucosa, 40% for normal muscle and 22% for normal mucosa. Substance P (50 μM) and compound 48/80 (100 μg/ml) induced ca. 30% of histamine release from normal muscle mast cells but only 11–13% from muscle mast cells of the diseased tissue.

Discussion

The present study has shown that mast cells isolated from the human bladder in the normal and diseased state behave differently in response to a range of secretagogues. The increased sensitivity of mast cells towards anti-human IgE in the diseased state may indicate that mast cells play an important role in the pathogenesis of IC [6]. The ability of mast cells, especially those isolated from the muscle of normal bladder, to respond to substance P, a neurotransmitter which has been found to be released from sensory nerve fibres in the vicinity of the bladder, suggests that there may be a phenotypical change of the mast cell in the diseased state due to microenviromental

Table 1. Effect of a range of secretagogues on mast cells isolated from the human bladder.

Secretagogue	Histamine release (%)			
	Normal		Interstitial cystitis	
	Mucosa	Muscle	Mucosa	Muscle
Anti-IgE (dilution)				
1/100	7.6±5.7	5.5±3.0	26.7±6.8	28.8±4.2
1/300	6.0±3.9	3.5±1.7	19.7±7.5	21.8±3.7
1/1000	2.9±2.9	1.6±0.7	11.3±5.8	10.9±2.9
1/3000	1.2±1.2	0.7±0.4	5.1±2.6	3.8±1.1
Ionophore A23187 (μM)				
3.0	14.3±5.5	32.7±2.3	41.3±7.9	32.0±5.4
1.0	17.8±5.9	40.7±10.1	51.2±6.7	63.2±6.5
0.5	22.3±8.4	38.5±11.0	40.0±8.6	68.0±5.0
0.3	19.1±6.3	32.2±12.1	39.3±9.2	67.4±4.7
0.1	14.6±10.3	5.2±2.5	7.3±3.9	28.1±9.3
Substance P (μM)				
50	ND	31.3±1.0	6.9±1.8	11.6±2.9
25	ND	24.6±4.0	6.3±2.0	8.9±3.1
5	ND	12.3±4.1	3.1±1.2	4.0±0.6
2.5	ND	3.8±4.0	1.4±0.7	3.3±1.4
Compound 48/80 (μg/ml)				
100	5.5±1.1	30.7±1.3	7.8±2.1	13.0±3.2
10	2.6±1.7	12.4±6.4	4.6±1.5	8.9±4.1
1	1.8±1.4	2.8±1.0	1.6±0.9	3.8±2.1

Values are means±SEM for 3–7 experiments. ND=not determined.

factors influencing the maturation and proliferation of the mast cell. These factors together may contribute to the cause or continuation of IC which may thus have neurogenic [7, 8] as well as allergic components.

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References

[1] D. Felsen, S. Frye and E. Darracot Vaughan, Jr., *Inflammatory mediators in interstitial cystitis.* Seminars in Urology *IX* 102–107 (1991).

[2] T. J. Christmas and J. Rode, *Characteristics of mast cells in interstitial cystitis.* Br. J. Urol. *68,* 473–478 (1991).

[3] J. T. Feltis, R. Perez-Marrero and L. E. Emerson, *Increased mast cells of the bladder in suspected cases of interstitial cystitis: A possible disease marker.* J. Urol. *138,* 42–43 (1987).

[4] H. Ali and F. L. Pearce, *Isolation and properties of cardiac and other mast cells from the rat and guinea pig.* Agents and Actions *16,* 138–140 (1985).

[5] G. Atkinson, M. Ennis and F. L. Pearce, *The effect of alkaline earth cations on the release of histamine from rat peritoneal mast cells treated with compound 48/80 and peptide 401.* Br. J. Pharmacol. *65,* 395–402 (1979).

[6] T. C. Theoharides and G. R. Sant, *Bladder mast cell activation in interstitial cystitis.* Seminars in Urology *IX,* 74–87 (1991).

[7] M. K. Church, M. A. Lowman, P. H. Rees and R. C. Benyon, *Mast cells, neuropeptides and inflammation.* Agents and Actions *27,* 8–16 (1989).

[8] T. Lundeberg, H. Liedberg, L. Nordling, E. Theodorsson, A. Owzarski and P. Ekman, *Interstitial cystitis: Correlation with nerve fibres, mast cells and histamine.* Br. J. Urol. *71,* 427–429 (1993).