

Review

Clinical consequences of mast cell heterogeneity

P. Forsythe and M. Ennis

Department of Clinical Biochemistry, Institute of Clinical Science, The Queen's University of Belfast, Grosvenor Road, Belfast BT12 6BJ, UK,
Fax: ++442890 236143, e-mail: m.ennis@qub.ac.uk

Received 1 July 1999; returned for revision 7 October 1999; accepted by M. J. Parnham 25 January 2000

Abstract. The heterogeneous morphological, biochemical and functional characteristics of mast cells from different species and from different tissue sites in the same species have been described for over 30 years. Far from being mere histochemical or pharmacological curiosities these differences have far reaching implications for therapeutic practice. This review concentrates on two important areas affected by mast cell heterogeneity, those of adverse reactions to therapeutic agents and the efficacy of anti-allergy therapy.

In vitro studies of preformed and de novo synthesised mediator release have demonstrated a wide variability in the response of basophils and isolated mast cells to anti-allergy drugs and therapeutic agents such as radiographic contrast media, general anaesthetics, opioids and muscle relaxants. This heterogeneity is not limited to the mast cell's tissue of origin as there is also variability in the response of basophils and mast cells from different donors to the same drug or agent.

These data have considerable clinical implications for the study of adverse drug reactions and the design of novel anti-allergic drugs.

Key words: Mast cells – Heterogeneity

Introduction

Mast cells were once thought to represent a single population of highly granulated secretory cells. However with the development of techniques for the isolation of mast cells from a diverse range of tissues, it became apparent that mast cells from different species and mast cells from different tissues within the same species exhibit variations in their biochemical, histochemical and functional properties.

Human and rodent mast cells are derived from multipotent stem cells in bone marrow [1]. Mast cell progenitors

may differentiate from either erythrocyte/megakaryocyte or monocyte/macrophage lineage [2]. However, because the repertoire of surface markers on mast cell precursors is not fully understood, the precise differentiation pathway is unclear. However some of the factors involved in differentiation have been defined. Human bone marrow mononuclear cells treated with recombinant interleukin (IL)-3 gave rise to mast cells while CD 34⁺ stem cells cultured with stem cell factor (SCF), IL-3 or 3T3 fibroblasts were shown to develop into mast cells [3, 4]. After mast cell progenitors leave the blood further differentiation occurs at the tissue site under the control of growth factors, cytokines and other factors [1]. In humans, SCF is the predominant cytokine involved in the maturation of mast cells [4]. However, other factors have stimulatory or inhibitory actions on mast cell maturation. IL-4 inhibits the expression of c-kit and tryptase by human fetal liver mast cell progenitors. As these progenitors mature they become less effected by IL-4 [5]. Stimulatory effects of IL-4 have also been described in conjunction with inhibitory effects of IFN- γ [6]. However, IFN- γ has been reported to promote the survival of human cultured mast cells and IL-4 has been shown to be inhibitory if added on the first 4 days of culture [7]. These studies suggest that factors influencing mast cell development may exert very different effects depending on the state of maturation of the cell that they come in contact with.

The concept of mast cell heterogeneity was established by Enerbäck in the mid 1960's through a series of detailed morphological and histochemical studies on the gastrointestinal tract of the rat [8]. Enerbäck noted that mast cells in the deeper layers of the intestinal wall or submucosa were very similar to those found in other connective tissues while those in the mucosa, confined mainly to the lamina propria, displayed numerous differences. These cells, designated mucosal mast cells (MMC) were smaller and more variable in shape than their submucosal counterparts. MMC contain lower levels of histamine, negligible 5-HT and fewer granules. MMC also contain the glycosaminoglycan chondroitin sulphate which is less sulphated and has lower overall

charge than heparin, the major proteoglycan in the connective tissue mast cell (CTMC) [9–12]. In humans the distinction between the two cell types is considerably more subtle than in the rat. The subpopulations are also no longer confined to particular anatomical regions, therefore it is inaccurate to assign a label of ‘mucosal’ or ‘connective tissue’.

A heterogeneity of neutral protease content exists within both rat and human mast cell populations. Rat CTMC contain the chymotrypsin-like neutral protease RMCP I and carboxypeptidase A, an enzyme that cleaves C-terminal aromatic amino acids. Rat MMC contain a different chymotrypsin-like neutral protease RMCP II [9–11]. Human mast cells consist of a population that contains measurable amounts of both tryptase and chymase and a second population that contains only tryptase. These cells are termed MC_{CT} and MC_T respectively [12]. The MC_T cells are predominant in the lung and the intestinal lamina propria, whereas the MCCT cells are the predominant cell in the skin and the intestinal submucosa. The distribution of MC_T and MC_{CT} cells suggests that they are broadly analogous to rat CTMC and MMC respectively. However, as more detailed studies of human mast cell heterogeneity have been carried out it has proved more useful to classify mast cells according to the specific tissue in which they reside rather than as CTMC/MMC or MC_T and MC_{CT}.

Functional heterogeneity

Specific tissue microenvironments profoundly influence the development and subsequent phenotypic expression of the mast cell. Mast cells are in close contact with a variety of cell types that can synthesise and secrete a diverse array of growth factors, histamine releasing factors, cytokines and chemokines, all of which may alter or determine the mast cell phenotype. More recently there has been an increased awareness of the cross talk between mast cells and both the nervous and endocrine systems, particularly the modulatory effect that neuropeptides and hormones may exert [13–15].

One aspect of heterogeneity in mast cell populations where the influence of anatomical location is clearly observed is in their response to stimuli. Human, skin mast cells release significant amounts of histamine when stimulated with compound 48/80, while adenoidal, colonic, lung and tonsillar mast cells are unresponsive [9–11, 16]. The neuropeptide substance P also causes significant histamine release from human skin and bronchoalveolar lavage (BAL) mast cells while having no effect on mast cells from most other tissues including those enzymatically dispersed from human lung [17].

Functional heterogeneity of mast cells has wide-ranging physiological and clinical implications. These implications are most evident in the response of mast cells to anti-allergy therapies or drugs that have the potential to produce adverse responses. With regard to these responses it is now apparent that information gathered from animal models, cell lines or human mast cells from one tissue type may not be applicable to the target mast cell populations.

Anti-allergic agents

The anti-allergic agents sodium cromoglycate (SCG) and nedocromil sodium (nedocromil) demonstrate a range of efficacies in inhibiting mediator release from human mast cells from different tissue sites. In mast cells dispersed from human lung, tonsillar and adenoidal tissue SCG and nedocromil are inhibitors of IgE mediated histamine and PGD₂ release [18]. However, human skin mast cells are unresponsive to both these agents, as are human basophils (Fig. 1) [18, 19]. The long term efficacy of these compounds is also dependant on the mast cell model used with both nedocromil and SCG showing tachyphylaxis in lung and tonsillar mast cells but not in mast cells dispersed from adenoidal and intestinal tissue [18].

Heterogeneity of mast cell responses to SCG and nedocromil has also been observed between different mast cell populations in the lung. Nedocromil is an order of magnitude more effective in suppressing histamine release from bronchoalveolar lavage (BAL) mast cells than from mast cells dispersed from lung tissue [20]. Furthermore tachyphylaxis to the inhibitory effects of nedocromil and SCG occurs only in the dispersed lung mast cell population (Fig. 2) [20].

β_2 -adrenergic receptor agonists suppress immunologically induced release of histamine and eicosanoids from dispersed human lung, skin and tonsillar mast cells and inhibit TNF release from human skin mast cells [21–23]. However despite the identification of abundant β_2 -adrenergic receptors on rat peritoneal mast cells, β_2 -agonists do not inhibit mediator release from these cells [24–26]. These data indicate that the heterogeneous responses of mast cells are influenced by factors more complex than differential receptor expression. This concept is supported by findings that the response of mast cells to immunological stimuli is not necessarily determined by the surface density of IgE receptors [27, 28].

Theophylline, a non-selective phosphodiesterase inhibitor, abrogates histamine release from human basophils, rat peritoneal mast cells and cultured murine mast cells [29–31]. At high concentrations (3 mM), theophylline inhibits immunologically-induced histamine release from a variety of human mast cells (Fig. 3). However, at concentrations of up to 100 μ M, theophylline does not inhibit IgE stimulated

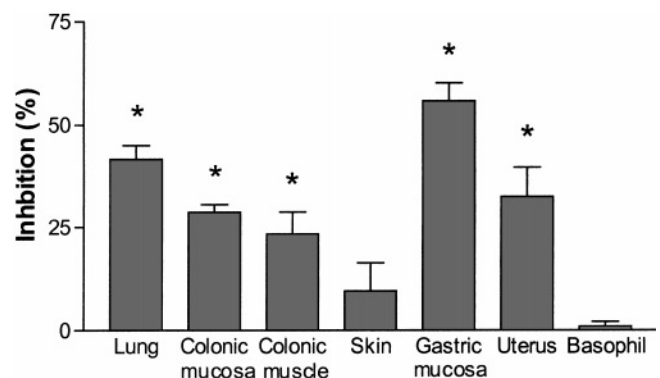


Fig. 1. Nedocromil (100 μ M) induced inhibition of anti-IgE induced histamine release from human mast cells and basophils. * p < 0.05 compared to unblocked release. Figure redrawn from data in Pearce FL et al. [19].

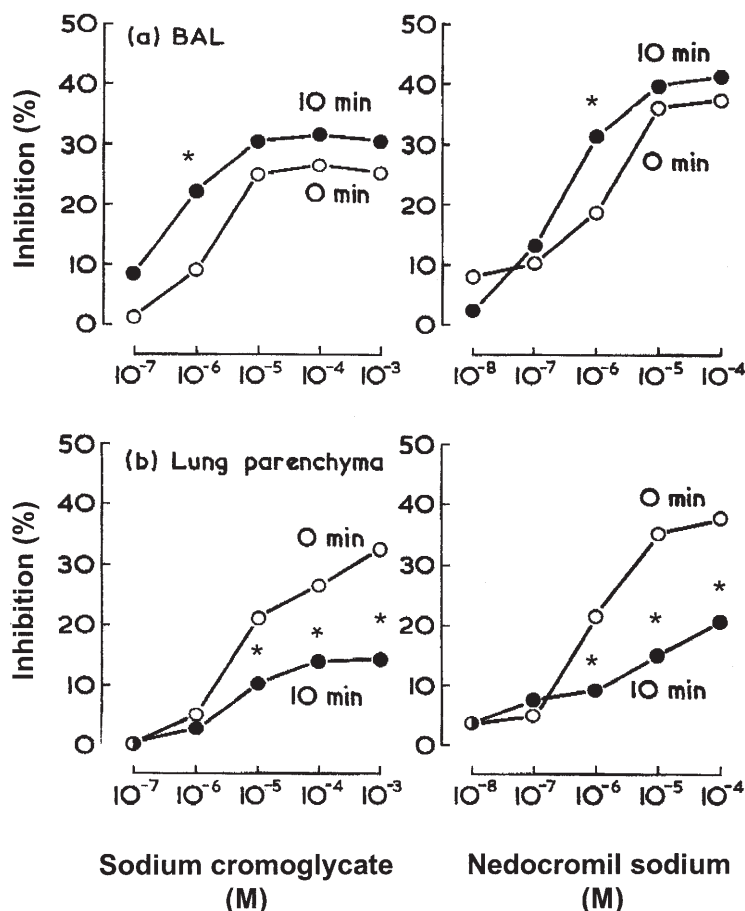


Fig. 2. Effect of preincubation with sodium cromoglycate or nedocromil sodium on the inhibition of immunologic histamine release from human pulmonary mast cells. Experiments with (a) bronchoalveolar lavage cells (BAL) were performed 8 times and experiments with (b) enzymatically dispersed lung parenchyma were performed 10 times. Standard error bars have been omitted for clarity. * $p < 0.05$ compared to 0 min preincubation. Data taken from Leung et al. [20] and unpublished work by Professor FL Pearce (University College London).

histamine release from either human lung fragments or cultured human mast cells [23, 32]. The phosphodiesterase 4 inhibitor, rolipram, inhibits histamine release from cultured human mast cells at high concentrations (100 μM) but does not cause significant inhibition of histamine release from human lung fragments at this concentration [23, 32].

The mucolytic agent ambroxol (trans-4-[2-amino-3, 5-dibromobenzylamino] cyclohexanol hydrochloride) has anti-inflammatory properties and inhibits bronchoconstriction in guinea-pigs. At high concentrations (1 mM), ambroxol significantly inhibits histamine release from human adenoidal mast cells [33]. In contrast, lower concentrations (100 and 500 μM) inhibit histamine release from human skin mast cells and 1000 μM increases the histamine release. In human basophils, the agent significantly inhibits histamine release from 10–100 μM and leukotriene C4 production at 50 and 100 μM . Higher concentrations were not tested on basophils.

This heterogeneity in the response of mast cells to anti-allergic agents demonstrates the problems involved in selecting cell models for the screening of mast cell-stabilising compounds and emphasises the need for putative therapeutic agents to be tested on models physiologically relevant to the targeted disorder.

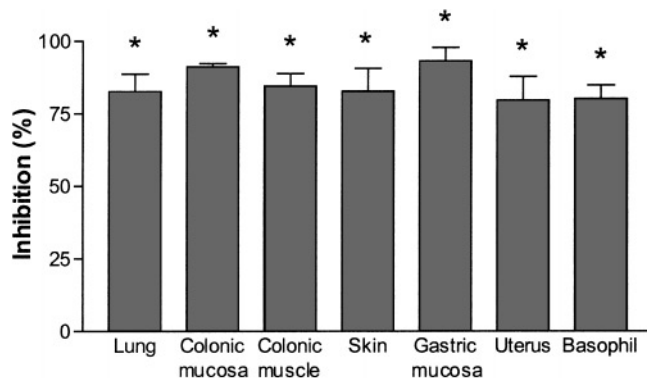


Fig. 3. Theophylline (3 mM) induced inhibition of anti-IgE induced histamine release from human mast cells and basophils. * $p < 0.05$ compared to unblocked release. Figure redrawn from data in Pearce et al. [19].

Adverse Reaction to drugs used in Diagnostic or Therapeutic Procedures

There are three principal mechanisms by which mast cells can be activated by drugs used in diagnostic or therapeutic procedures. Drugs can induce anaphylactic mediator release by crosslinking specific IgE molecules bound to the surface of the mast cell. Specific IgE antibodies have been identified for muscle relaxants, opioids and hypnotics such as thiopental [34–37]. Alternatively drugs can activate the complement cascade; either via the classical pathway, complement fixing IgG or IgM antibodies or through direct interaction with the C3 component [38–40]. The latter results in the formation of anaphylatoxins that in turn activate the release of histamine from mast cells [41–44]. Finally, drugs may also elicit histamine release via direct activation of the mast cell. However compounds most associated with anaphylactic/anaphylactoid reactions appear to act through a combination of the above mechanisms.

Radiographic Contrast Media

Although valuable diagnostic aids, infusion of radiographic contrast media (RCM) represents the major cause of anaphylactoid reactions in modern medical practice. Most of the RCM currently used are ionic agents, derivatives of triiodinated benzoic acid, administered at an osmolarity 3–5 times that of plasma [45]. Hyperosmolarity is probably responsible for some of the adverse effects of these substances [46–48]. The use of lower osmolarity RCM does result in a decreased incidence of reactions compared to hyperosmolar agents [46, 47]. The anaphylactoid reactions observed following administration of RCM range from dyspnea, urticaria, pruritus, angioedema, to hypotension or shock [49]. Both in vivo and in vitro experiments provide strong evidence that histamine release from mast cells and basophils plays a role in these adverse reactions [50–55]. Reports have suggested that RCM activate mast cells through complement activation by production of anaphylatoxins [53, 54] or via direct activation of the cells via an as yet unknown mechanism [46, 49]. RCM are partial secretagogues of mast cells and basophils inducing only the release of preformed mediators without stimulating the de novo synthesis of eicosanoids, a fact which explains the efficacy of H_1 and H_2 receptor antagonists in preventing RCM induced adverse reactions [56].

RCM activate not only peripheral blood basophils but also isolated human mast cells. However it is clear that human mast cells isolated from different tissues are heterogeneous in their responses to different RCM. RCM induce histamine release in a dose dependent manner from human heart and lung mast cells but do not cause the activation of skin mast cells in vitro [57]. The activation of the human heart mast cells by RCM is of particular clinical relevance as it has been demonstrated that patients with cardiovascular disease are at increased risk of RCM induced adverse reactions [48, 57]. Intravascular injection can induce coronary artery spasm, hypotension and shock [47, 48]. A direct effect of vasoactive mediators released from cardiac mast cells may contribute to the clinical manifestations of RCM-related reactions. Mast cell density is high in the atherosclerotic

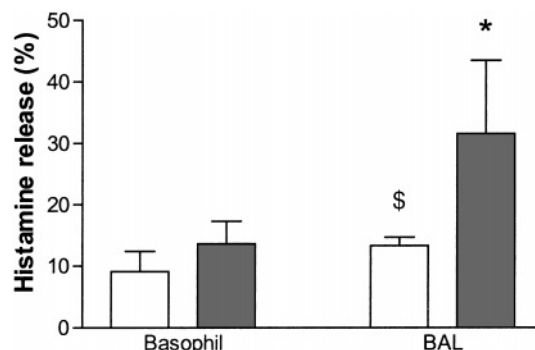


Fig. 4. Comparison of histamine release induced by the radiographic contrast media Iohexal (open columns) and Urographin (filled columns) (both 350 mM) from human basophils and bronchoalveolar lavage cells from the same donors. * $p < 0.05$ Urographin induced histamine release from bronchoalveolar lavage cells versus basophils. \$ $p < 0.01$ Iohexal versus Urographin induced histamine release from bronchoalveolar lavage cells. Data are presented as mean $\pm$ SEM and taken from Ennis et al. [61].

intima [59] and during coronary angiography it is likely these cells are exposed to high concentrations of RCM.

Anaphylactoid reactions to RCM often involve the skin with flushing, pruritus and urticaria [47, 49]. The poor in vitro response of skin mast cells to RCM suggests that these reactions involve complement activation and anaphylatoxin formation that may trigger skin mast cell degranulation in vivo [47, 50, 60].

Studies have demonstrated that hyperosmolarity may be more important in inducing histamine release from basophils than from mast cells as a correlation between histamine release and osmolarity is apparent in basophils but not in mast cells [57, 60]. Indeed while agents of low osmolarity Hexabrix and Optipray have been demonstrated to induce concentration dependent histamine release from human lung parenchymal mast cells; Telebrix, a high osmolarity RCM which activates basophils, did not induce histamine release from human lung mast cells [57, 60]. The effects of the RCM Iohexal and Urographin have been assessed in basophils and BAL mast cells from the same donors [61]. While a high degree of inter-donor variation was observed in both cell types, BAL mast cells were more responsive to the compounds, particularly Urographin, than were basophils (Fig. 4). Furthermore the response of a donor's basophils could not be used to predict the effect of the same compound on BAL mast cells [61]. This highlights a potential difficulty of in vitro testing for anaphylactoid responses to drugs. A negative result from one mast cell type cannot be extrapolated to mast cells from different anatomical sites even within the same patient.

General Anaesthetics

Anaphylactic/anaphylactoid reactions can occur during the intravenous administration of general anaesthetics and there is evidence that many of these compounds can induce histamine release from mast cells and basophils [62–64]. The short acting barbiturate thiopental was one of the first drugs

used in anaesthesia reported to cause adverse reactions [64]. Thiopental induces basophil and mast cell activation involves both immunological and non-immunological mechanisms [63, 65–67]. The non-barbiturate drug propofol does not induce histamine release from normal human basophils but causes dose dependant activation of human lung mast cells at pharmacological concentrations [63]. Human skin mast cells are much less responsive to this drug. Like RCM general anaesthetics act as incomplete secretagogues of human mast cells causing release of histamine and tryptase but not stimulating the *de novo* synthesis of eosinoids [54].

Muscle Relaxants

Muscle relaxants are the most frequent cause of reactions during general anaesthesia. These compounds can act via IgE-mediated activation of mast cells. The tertiary or quaternary ammonium group is the main allergic determinant. The two IgE-binding epitopes in each molecule enable these compounds to bridge specific IgE on mast cells and basophils without the need for carrier molecules thus acting as true allergens [68]. However a significant percentage of adverse reactions to muscle relaxants are due to direct activation of the mast cell [69]. Mast cells from different anatomical sites show marked heterogeneity in their response to different muscle relaxants. Atracurim and vecuronium dose dependently induce mediator release from human skin and lung mast cells. Only high concentrations of d-tubocurarine ($>10^{-3}$ M) will activate the same cells while suxamethonium does not induce mast cell mediator release [70].

Opioids

Human mast cell populations also vary in their response to opiate drugs. Morphine induces mediator release from human skin mast cells but not from lung, heart, intestinal mast cells or basophils [71–74]. There is, however, marked heterogeneity in the effects of other opioid drugs on human mast cells. In contrast to morphine, buprenorphine causes histamine and tryptase release from lung but not from skin mast cells. Further, buprenorphine induces the *de novo* synthesis of PGD₂ and LTC₄ from lung mast cells while morphine acts an incomplete secretagogue on skin mast cells, with the response limited to the release of preformed mediators [60, 74]. The synthetic phenyl piperidine, fentanyl does not induce mediator release from isolated skin, heart and lung mast cells or human basophils [75].

Inter-patient variation and the concept of releasability

In humans, there is considerable donor to donor variation in the response of mast cells to stimuli. Such heterogeneity is clinically relevant as the same dose of a drug can produce differing responses from patient to patient. This is reflected in the wide range of severity of clinical manifestations observed during adverse drug reactions and the unpredictability of an individual's response to these compounds [49]. This phenomenon may be attributed the releasability of the patients'

mast cells. Releasability is a term used to describe the ability of inflammatory cells to release their mediators. The term was first utilised in 1976 by Lichtenstein and Conroy [76], and was applied to the *in vitro* study of chemical mediator release from human basophils, although the phenomenon had been described some two years previously by Assem [77]. The releasability of a mast cell or basophil is influenced by a number of complex genetic and environmental factors [77–79]. The parameter of releasability must be defined in relation to the stimulus employed as there appears to be no correlation between the sensitivity and reactivity of cells to release with any of the commonly used immunological and non-immunological stimuli [80].

The releasability of mast cells to immunological stimuli is not necessarily determined by the surface density of IgE on the cell [27, 28]. It has been demonstrated that different rat strains with similar levels of IgE and IgE receptors on the cell may have significantly different histamine releasability when stimulated with anti-IgE antibodies [27]. This indicates that genetic factors may regulate the secretory capacity of the cell by means other than IgE receptor expression or IgE production; influencing steps in the signal-release coupling pathway such as cytosol kinases.

The local microenvironment of mast cells presents a complex milieu of cytokines, growth factors, chemokines, integrins and neurogenic stimuli of which the full impact on mast cell releasability is unknown. IgE mediated histamine release from mast cell in athymic rats is significantly less than that of euthymic rats even when IgE receptor and IgE levels are similar [28]. This suggests T-cell factors are involved in the regulation of the IgE mediated signal transduction leading to histamine release.

Spontaneous histamine release is defined as histamine release which occurs as a result of unspecified environmental stimulation by physical and chemical factors during experimental procedure. Blood basophils of atopic dermatitis patients have an increased spontaneous release as well as an increase in IgE-dependent and calcium ionophore induced release compared to control subjects [78]. Spontaneous histamine release is also increased in rat strains which exhibit a high releasability to IgE mediated stimulation compared to strains with low releasability [27]. It is therefore possible that spontaneous release may be under the control of the same genetic and environmental factors that influence the releasability of stimulated mast cells. It is also suggested that spontaneous histamine release may prove an important indicator of immuno-pathological and atopic conditions [27].

Inter-individual variation in the response of BAL mast cells to non-immunological stimuli is also prevalent. The ability of adenosine to augment histamine release induced by both immunological and non-immunological stimulation of mast cells is well documented [81–85]. More recently it has been demonstrated that adenosine alone can induce histamine release from human BAL mast cells [86]. However the response to adenosine is not universal with 37 of 54 reported donors showing no increased histamine release in the presence of the nucleoside. Where adenosine induced histamine release is observed there is a remarkable degree of inter-donor variation in both the degrees of response and the concentration of adenosine eliciting maximal release (Fig. 5). The reasons for the variability of response to adeno-

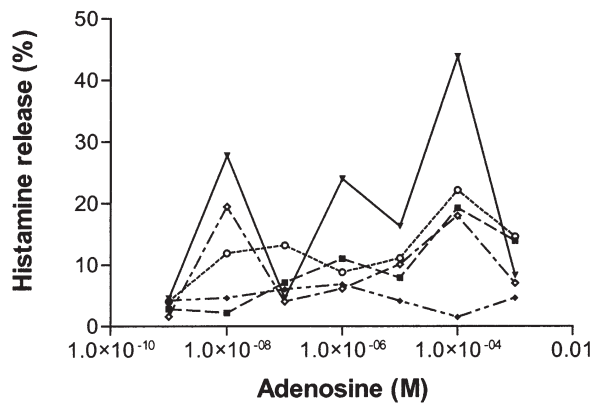


Fig. 5. Comparison of adenosine-induced histamine release from human bronchoalveolar lavage mast cells. Individual patient responses are shown. Data taken from Forsythe et al. [86].

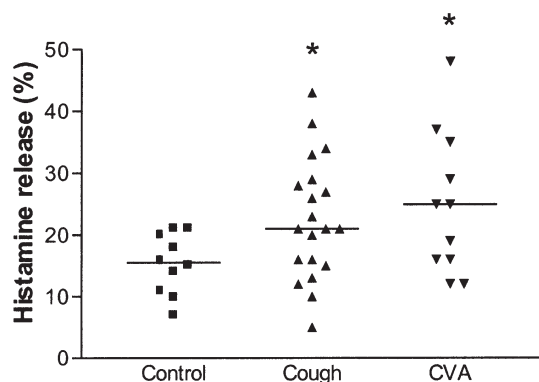


Fig. 6. Histamine release induced by CGRP (50 μ M) from human bronchoalveolar lavage mast cells. Individual patient responses are shown. Cough = patient with chronic non-productive cough. CVA = patient with cough variant asthma. * $p < 0.05$ compared to control. Data taken from Forsythe et al. [89].

sine are unclear however, the effects of patient medication, prevalence of adenosine receptor subtypes on the cell surface and influence of other mediators in the cell's microenvironment may all play a role [86].

Inter-donor variation is also revealed in the response of human BAL mast cells to neuropeptides. Substance P, neurokinin A, calcitonin gene related peptide (CGRP) and bradykinin all induce histamine release from BAL mast cells. However the degree of histamine release induced by any one of these neuropeptides is dependent on the donor (Fig. 6) [87–89].

Influence of disease states

Given the profound influence of tissue microenvironment on the mast cell it is unlikely that the releasability of a specific mast cell population within an individual remains static. Changes in the extracellular milieu brought about through infection and disease will alter the ability of the cell to respond to stimuli. IgE mediated histamine release is greater in BAL mast cells from mild asthmatics than from normal

controls [90, 91]. More recently additional functional differences have been demonstrated. BAL mast cells from patients with asthma and chronic non productive cough have an increased response to substance P and CGRP respectively (Fig. 6) [87, 89].

Conclusions

Mast cell heterogeneity is a complex phenomenon. Mast cells from different species, from different sites in the same species and even from the same organ in one species can vary in their response to stimuli and inhibitors of mediator release. In the clinical situation, the effects of the underlying disease further complicate this heterogeneity of response. Furthermore, although mast cell activity is commonly demonstrated by the measurement of histamine release, mast cells secrete a host of other mediators including cytokines, leukotrienes and prostaglandins. Some agents implicated in adverse drug reactions have been shown to cause a selective release of the different mediators from human mast cells. Although basophils are the most readily available human histaminocytes, their use in the investigation of adverse drug reactions or new anti-allergic drugs is limited. Cultured human mast cells raised from cord blood mononuclear cells are now available and their response to stimuli and inhibitors of activation resembles that of human lung mast cells [92]. Since the mast cell phenotype is dependent on its microenvironment, modulation of culture conditions may enable the selective growth of phenotypically different mast cell populations. This approach may be invaluable in the study of anti-allergic drugs and adverse drug reactions.

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