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AGENTS THAT RELEASE HISTAMINE FROM MAST CELLS

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INTRODUCTION

A fully differentiated mast cell, packed with 500 to 1000 granules, poised for secretion, wants only the appropriate stimulus to release the contained histamine, heparin, and hydrolytic enzymes into the connective tissue. Since the major storage site of histamine in mammalian tissues was located in the mast cell by Riley & West (1), the cell has been a major focus in the study of histamine release. The literature is abundant and there is no dearth of reviews (2–7) and books (8–10) on the mast cell and its histamine-releasing activities.

We concentrate in this review on agents of more or less known structure capable of releasing histamine, and attempt to collect information on a range of agents and to evaluate succinctly the available information on their modes of action. The behavior of mast cells in response to a few agents has been studied in considerable detail, and we stress these as archetypes. The important category of IgE-mediated release has recently been reviewed in this series (11) and elsewhere (12, 13) and will not be considered here.

Under usual conditions, virtually all of the histamine stored in mast cells is located in the cells' secretory granules (14, 15, 16). These granules in the rat consist of a matrix of heparin and a limited number of proteins (17) of which only two, both mast cell proteases, have been characterized substantially (18, 19). Histamine and several acid hydrolases are weakly associated with the matrix by ionic bonding (20, 21); some unbound histamine may

also be present within the granule membrane. Histamine to be released from the mast cell must cross the perigranule membrane and the cell membrane. In cytotoxic release, histamine escapes when the integrity of the two membranes is compromised; in secretory release, fusion of the two membranes creates a passage to the outside for histamine without disturbing cell viability.

Variants of the classic exocytotic mode of secretion have been postulated for the mast cell and basophil. Displacement of histamine from its granule binding site with molecular leakage across the two membranes has been invoked to explain release by chlorpromazine (22, 23) and the ionophore X537A (24), and vesicular ferrying of histamine from storage granule to cell surface has been proposed on the basis of electron microscopic observation of basophils in lesions of delayed hypersensitivity (25). However plausible such mechanisms may be, strong evidence for these alternatives has not yet been provided. The recent description of selective release of serotonin relative to histamine in the presence of amitriptyline is provocative (26). More information on the intracellular distribution of serotonin is necessary to begin to analyze this finding.

ANALYSIS OF HISTAMINE RELEASE

The study of histamine-releasing agents in humans has progressed from evaluation of pathophysiologic changes attributable to histamine to the assessment of increases in plasma histamine levels. The circulating human basophil has lent itself to the measurement of histamine release in in vitro systems. The problems of obtaining adequate numbers of these leukocytes in adequate homogeneity for direct biochemical studies have not yet been surmounted (27, 28). Methods for obtaining an almost homogeneous population of human lung mast cells have been developed (29), but their general usefulness is likely to be limited by problems attendant on obtaining surgical specimens and by low yields of mast cells. Rat peritoneal mast cells are the mainstay of detailed studies of the mechanism of histamine release. The prevalent use of these cells should not obscure the likelihood of significant differences between human and rat mast cell responses. Major discrepancies in the activity of various releasing agents in different species are well known (30, 31).

For quantitative measurements of secretagogue binding and study of the actual events of secretion, pure populations of mast cells or basophils are of course essential, and methods are now available to prepare both cells in reasonable purity, if limited yield. In 1955 Padawer & Gordon (32) first described a method for the isolation of mast cells obtained from the rat peritoneal cavity; the concentrated sucrose solutions they used led to major

losses of histamine during the procedure, and little or no release occurred on exposure of the cells to agents expected to cause histamine release. In 1959, three laboratories independently reported the use of high molecular weight polymers in place of sucrose. Archer (33) and Lagunoff & Benditt (34) used bovine serum albumin, and Uvnäs & Thon (35) used ficoll. Both of these substances have since been widely applied to the isolation of peritoneal mast cells. Two other high density media have been introduced more recently: metrizamide by Lynch, Austen & Wasserman (36), and percoll by Nemeth (37) and Enerbäck & Svensson (38). Since it has been shown that mast cells are the only source of histamine in the population of rat peritoneal cells, many experiments can be conducted without separating mast cells from the other cells. Occasionally mast cells from guinea pigs and hamsters have been similarily studied, whereas rat basophils are disappearingly infrequent. Guinea pig basophils are moderately abundant, and a method has been developed for their isolation from bone marrow and blood (39). Morphologic examination of guinea pig basophils has tended to be more extensive than biochemical or physiological studies.

A secreting subline of the rat basophil leukemia cell line (RBL) identified by Siraganian et al (40) has seen considerable use in recent years in the study of histamine release (41). The majority of studies in RBL cells have been devoted to the role of IgE and IgE receptors in secretion, but other secretagogues have been examined. In view of the availability of large numbers of these cells, it is unfortunate that neither the intracellular localization of histamine nor the mode of release has been defined.

Two chemical methods for the measurement of histamine have virtually replaced the bioassay. The method utilizing the fluorescence of an o-phthalaldehyde (OPT)-histamine adduct was introduced by Shore, Burkhalter & Cohn (42). Under most conditions its specificity and sensitivity are adequate. Interfering substances can frequently be eliminated by extraction procedures, ion exchange chromatography, or HPLC. Snyder, Baldessarini & Axelrod (43) developed an alternative assay that uses a highly specific histamine N-methyl transferase to fix a radioactive methyl group to the histamine. Separation of N-methyl histamine and S-adenosyl methionine then allows direct quantitation of the radioactive histamine derivative. Inhibitors of the enzyme can be a nuisance in this procedure. Enzymic methylation of histamine prior to the formation of the OPT adduct has been used to test for the specificity of the OPT reaction under special circumstances, as has the heat lability of the product (44).

There is considerable agreement among investigators that in most instances of noncytotoxic histamine release from mast cells there is a common final pathway. It is a working hypothesis that most secretagogues bind to receptors borne on the cell surface and induce, through a variable sequence

of steps, a change in the free cytoplasmic Ca^{2+} concentration, the signal that invokes the final common pathway culminating in exocytosis. Events in the secretory process under active study include proteolysis (45), phospholipid methylation (45), protein kinase activation (46), protein phosphorylation (47–49), endogenous phospholipase A_2 activity (50–52), and calcium channel perturbation (11). The details of the integrated system remain obscure.

The range of agents capable of eliciting histamine release is impressive. In order to deal with the substantial array of entities, it is useful to have a classification system. In Table 1 we compare Paton's classical system, proposed in 1957 (2), with a modification we have used in this review.

ENZYMES

In the pioneering studies of Högberg & Uvnäs (53) on the actions of potential secretagogues on mast cells in vitro, a single enzyme of a modestly long list tested was active in inducing histamine secretion: phospholipase A_2 (PLA_2). Subsequently Fredholm (54), in 1966, found that the histamine-liberating action of the PLA_2 preparation from bee venom used in Högberg & Uvnäs's study was attributable to a polypeptide, and showed that the PLA_2 was inactive. The responsible agent was subsequently separated from the major peptide, mellitin, in bee venom (55), and named mast cell degranulating peptide (MCD), or peptide 401. Fredholm's observation discouraged the further use of PLA_2. In 1978, Whelan (56) published results indicating that PLA_2 was effective as an enzyme but that the effect was mediated through the formation of lysolipids, which were cytotoxic, lytic releasers of mast cell histamine. To bring the story completely around, Chi & Henderson (57) have recently presented convincing evidence that pig pancreatic PLA_2 purified to homogeneity can noncytotoxically release mast cell hista-

Table 1 Classification of agents that release histamine

Paton's classification (2)	New classification
1. Sensitizing agents	a. IgE receptor dependent agents
2. Agents damaging tissues	b. Cytotoxic agents
3. Proteolytic enzymes	c. Enzymes (cytotoxic agents)
4. Surface active agents	
5. Large molecules	d. Polysaccharides
	e. Lectins
	f. Anaphylatoxins
6. Histamine liberators	g. Polybasic compounds
7. Monobasic compounds	h. Paucibasic compounds
—	i. Calcium
—	j. Other compounds

mine by stimulation of the classical exocytosis mechanism. They have further shown that enzymatic activity is required, as modification with bromophenacyl bromide of a single, essential histidine residue destroyed enzyme activity and histamine-releasing activity simultaneously.

Martin & Lagunoff (52) have recently demonstrated that rat mast cells have an active PLA_2 and that inhibition of this enzyme is paralleled by a loss of the ability of the mast cell to respond to several histamine-releasing agents. Before a role of endogenous PLA_2 in the cells' secretory mechanism can be seriously considered, more detailed studies, particularly with a specific range of inhibitors, are necessary.

The saga of chymotrypsin, in contrast to that of PLA_2, is straightforward. This protease releases histamine in a noncytotoxic mode, and enzyme activity is necessary for histamine-releasing activity (58). At nontoxic concentrations trypsin releases very little histamine, and pretreatment of cells with trypsin makes them refractory to chymotrypsin.

There is a large store of an active protease in rat mast cells, with a substrate dependence much like that of bovine α-chymotrypsin (18). The enzyme is restricted to the secretory granules, and its virtually complete inhibition is without effect on subsequent secretion. Based on the inhibitory effects of inhibitors of α-chymotrypsin, a second protease has been proposed for the mast cell. This enzyme is putatively activated by secretory stimuli and has been proposed as a critical element in the secretory process (45).

The only other enzyme for which there is convincing evidence indicating an ability to cause secretory release of histamine from mast cells is eosinophil peroxidase (59). For its releasing activity the enzyme requires both hydrogen peroxide and halide ions. This activity obviously means that when attempting to iodinate mast cell surface proteins, one needs to inactivate the secretory mechanism before commencing the labeling procedure. Hydrogen peroxide at higher concentration can alone release histamine noncytotoxically (60). The histamine-releasing activity of xanthine oxidase is apparently dependent on the generation of hydrogen peroxide (61, 62).

POLYSACCHARIDES

The advent of dextran as a plasma expander (63) stimulated investigation of its effects in experimental animals and led to the description of its toxicity in albino rats (64). Injection of dextran into rats by several routes produced edema, pruritis, and systemic vascular collapse. These effects were associated with a large increase in plasma histamine levels and were prevented by the prior administration of antihistamines (65). Subsequent studies verified the ability of dextran to degranulate rat mast cells in vivo (66, 67). The toxic effects of dextran related to histamine release have been observed only

in rats. The medium-sized dextrans (MW 30,000–300,000) are in general the most potent (65). The response of rats to dextran has since been shown to be a heritable trait, and nonresponder strains have been selected (68). Dextran also fails to induce histamine release in diabetic rats (69, 70) or when injected into normal rats simultaneously with certain specific mono- and disaccharides (71, 72). Glucose competitively inhibits dextran-induced histamine release from isolated rat mast cells (73, 74).

Although dextran induced rat mast cell degranulation and histamine release in vivo, in initial studies it did not release histamine from rat peritoneal mast cells in vitro (75). However, the addition of phosphatidylserine (PS) to the incubation medium restored in vitro responsiveness of isolated rat mast cells to dextran (76). Baxter et al have established that dextran-induced histamine release from rat mast cells in the presence of PS resembles antigen-induced release in its temperature dependence and its inhibition by certain pharmacologic agents (77, 78). A consistent finding by these workers (78, 79) and others (80, 81, 82, 83) is the strict dependence of this response on extracellular Ca^{2+}, which is required both for activation of histamine release and for induction of cell desensitization. Experimental evidence indicates that PS may enhance histamine release from isolated rat mast cells by delaying the onset of cell desensitization, which occurs rapidly in cells exposed to dextran and Ca^{2+} in the absence of PS (84, 85). Dextran-induced histamine release from isolated mast cells is competitively inhibited by glucose (73, 74), but as yet binding of dextran to mast cells has not been demonstrated, and the character of the implied dextran receptor remains undefined.

Of several other polysaccharides tested for their ability to release histamine from rat mast cells, only dextrin (86) and mannan (74) have been shown to be effective agents. Histamine release by mannan is inhibited by mannose (74). Dextran occasionally elicits toxic reactions in humans, but these effects are not attributable to histamine release (87).

LECTINS

Lectins are hemagglutinins widely distributed in nature that possess saccharide-specific binding sites (88). Keller (89) first demonstrated that concanavalin A (Con A), a lectin isolated from jack beans, releases histamine from peritoneal mast cells obtained from parasite-infested rats. Con A has since been shown to release histamine from rabbit platelets (90), from human, rabbit, and guinea pig leukocytes (90), and from rat (91–93), mouse (90), human (31), and hamster (94) mast cells. Lectins isolated from wheat germ, castor beans, *Glycine max,* and lentil release histamine from rat mast cells (95–97), and phytohemagglutinin releases histamine from hamster mast cells (94) and human leukocytes (98).

The characteristics of Con A-induced histamine release from rat mast cells have been investigated in detail (89, 91, 92, 99–103). The accumulated data have established several factors to be critical determinants of the effectiveness of Con A as a histamine-releasing agent. Included among these factors are the strain of rat, the presence or absence of extracellular Ca^{2+}, the degree of cell sensitization, and the presence or absence of exogenously added phosphatidylserine. Unfortunately, no one study has adequately evaluated the relative effects of each of these variables on the overall release reaction. Nevertheless, it is clear that Con A-induced histamine release from rat mast cells and human basophils is noncytotoxic, occurs by exocytosis, is temperature-dependent, requires adequate stores of cell Ca^{2+}, and is inhibited by monosaccharides to which Con A binds specifically.

The evidence is strong that Con A-induced histamine release from basophils is mediated through its interaction with saccharide moieties located in the Fc region of IgE (104–107). Since Con A is tetravalent at physiological pH, it is postulated that this interaction crosslinks adjacent IgE molecules on the surface of the basophil much in the way that specific antigen crosslinks cell-bound IgE through its interaction with the antigen-combining sites of IgE. This mechanism may partially explain the action of Con A on sensitized rat mast cells, but it is possible that Con A induces histamine release through interaction with saccharide moieties on cell surface molecules other than IgE, as it effectively activates cells obtained from nonimmunized rats (91, 92), or preincubated under conditions known to remove cell-bound IgE (92).

Several workers have investigated the effect of wheat germ agglutinin (WGA) on rat peritoneal mast cells. In one study (96), WGA was shown to induce mast cell degranulation in the absence of extracellular Ca^{2+} and exogenous PS. This response was inhibited by monosaccharide-specific WGA haptens or by pretreatment of the cells with 2 mM EGTA for 3 h at 37°C. Others (97) were unable to obtain release of histamine from WGA-treated rat mast cells in the absence of extracellular Ca^{2+}, and significant release was dependent upon the presence of added Ca^{2+} and PS. The discrepancy in these results has not as yet been resolved.

ANAPHYLATOXINS

Anaphylatoxins are extremely potent biologically active polypeptide cleavage fragments derived from complement components C3, C4, and C5, designated C3a, C4a, and C5a, respectively, that elicit anaphylactoid reactions in vivo (108, 109). Early experiments established that infusion of activated complement released histamine from guinea pig lung (110) and degranulated guinea pig mesentery mast cells (111). Later experiments demonstrated the ability of human C3a to release histamine from isolated

rat peritoneal mast cells (112, 113). Others have confirmed the ability of C3a to degranulate mast cells in human skin (114, 115), and comparative studies have shown C5a to be 1000-fold more potent in this regard than C3a (116).

Using the indirect immunofluorescence technique, ter Laan et al (117) studied the binding of C3a to rat peritoneal mast cells. Whereas binding of C3a was readily demonstrable on cells treated with C3a in the presence of EDTA or cromoglycate, agents that inhibited degranulation, little C3a was detectable on mast cells degranulated by C3a. Experiments by Johnson et al (118) established that histamine release from rat peritoneal mast cells by C3a and C5a was noncytotoxic, temperature- and Ca^{2+}-dependent, and abolished by prior treatment of the anaphylatoxins with carboxypeptidase B. Histamine release by C3a and C5a was additive and potentiated by exogenous phosphatidylserine (PS). The des-Arg derivative of C3a partially inhibited release by native C3a. Binding studies performed with radioiodinated C3a and C5a indicated nearly equivalent numbers of binding sites on mast cells with apparent saturation binding at approximately 10 pmole/10^6 cells.

Activation of human serum with zymosan or antigen-antibody complexes leads to the formation of a component, presumably C5a, that releases histamine from human basophils (119, 120). Partially purified hog C5a also releases histamine from human leukocytes (121). Histamine release from human basophils by anaphylatoxin is noncytotoxic, requires extracellular Ca^{2+}, is temperature- and energy-dependent, and is inhibited by agents that purportedly increase intracellular cyclic AMP such as theophylline, prostaglandin E_1, and isoproterenol (119–124). Anaphylatoxin-induced histamine release from basophils is inhibited by colchicine and augmented by cytochalasin B (124, 125). Many of the characteristics of anaphylatoxin-induced histamine release thus resemble IgE-mediated release, and a recent ultrastructural study has established that C5a-induced histamine release from basophils occurs by an exocytotic process qualitatively identical to that triggered by IgE-directed agents (126). In contrast to IgE-directed agents, release by anaphylatoxin is more rapid (119, 121, 123) and is additive with IgE-induced release (123). Furthermore, there is no cross-desensitization between IgE-directed agents and anaphylatoxin (121–123).

Evidence exists to support the concept that the effects of C3a and C5a on human leukocytes are mediated through interaction with distinct receptors. Direct binding studies indicate that C3a cannot compete with C5a for binding sites on human leukocytes, and C3a binds preferentially to eosinophils and basophils whereas C5a binding is more selective toward neutrophils and eosinophils (127). Histamine release by C3a and C5a is additive, with C5a being the more potent releasing agent (128).

BASIC COMPOUNDS

Many basic compounds, including a large number of drugs, can release histamine from mast cells, and these have been catalogued in earlier reviews (2, 129). We do not add another list but stress recent work that provides information on the mechanism of the release reaction by basic compounds.

Compound 48/80

Although several histamine-releasing chemicals and drugs had been reported prior to the use of compound 48/80, and over a hundred have been identified since, the potency of 48/80 and the reproducibility of its effects have led to its intensive use as a prototype of polycations that release histamine. Despite the important role it has played, the structures of the active components in the mixture have not been definitively determined.

48/80, a mixed polymer of phenethylamine cross-linked by formaldehyde, was actually a by-product of efforts to synthesize a hypotensive tetrahydroisoquinoline (130–132). The powerful depressor action of 48/80 was shown to be caused by the release of endogenous histamine (133). Subsequently this release was identified as secretory and not lytic (134). Initially it was proposed that the trimer and the tetramer were the active species (131), but when these polymers were synthesized by an alternate route, they were found to be inactive (135, 136). When dialysis rates and gel filtration were used to estimate the molecular weight of the active polymers, the depressor activity was found to be associated with the tetrameric through the octameric derivatives, with peak activity associated with the hexamer (137).

The use of molar concentrations in reports on 48/80 is inappropriate as an appreciable amount of the commercially available mixture is inactive and the ratio of polymers is rarely determined. Preparations of 48/80 enriched with respect to the hexamer are three times as potent as the crude mixture (A. Hall and G. W. Read, unpublished). Another complexity that confounds work with 48/80 is the possibility that polymers of tetrahydroisoquinoline are present in the preparation (137, 138), since an oligomer of tetrahydroisoquinoline has been found to be a potent histamine-releasing agent (137).

Other Polybasic Histamine Releasers

The generalization is justified that virtually any polycation not overly laden with anionic sites can cause histamine secretion. Several characteristics of histamine secretion induced by 48/80 are shared by a group of oligo- and polybasic compounds. These include relative resistance to inhibition by micromolar concentrations of disodium cromoglycate (138), lack of poten-

tiation by phosphatidylserine (139), ability to induce secretion in calcium-free media (140), competitive antagonism by benzalkonium chloride (BAC) (141), inhibition by prior heating of the cells to 50°C for 15 min (142), and very rapid release.

Basic polypeptides as a group include a number of highly active histamine releasing agents (Table 2). Simple oligo- and polypeptides of lysine or arginine also have histamine-releasing activity (Table 3). All of these polypeptides are noncytotoxic, and bradykinin, polylysine, and substance P have been shown to share the property of inhibition by benzalkonium chloride with 48/80 (141). Arginine residues seem to be more effective than lysine residues, and the diaminobutyric moieties in polymyxin B are quite potent (Table 2). The greater the number of basic groups, in general, the more potent the agent over a limited range probably not exceeding 6 (Tables 2 and 3). Packing of the basic groups is probably also important although

Table 2 Polypeptide releasing agents[a]

Polypeptide	Total residues	Basic residues	Basic nodes	ED_{50}[a]	References
Polymyxin B	8	5	3	8×10^{-7}	143
				1.5×10^{-5}	145
Bradykinin	9	2	2	3×10^{-5}	144
				5×10^{-5}	143
Lys-bradykinin	10	3	2	1×10^{-5}	144
Met-lys-bradykinin	11	3	2	8×10^{-6}	144
				2×10^{-6}	144
Substance P	11	2	2	5×10^{-6}	145
				1.5×10^{-5}	146
					145
					147
Neurotensin	13	3	2	—[b]	148
					149
Somatostatin	14	2	2	1.5×10^{-6}	150
					151
Polistes kinin	17	6	4	3×10^{-6}	144
MCD (Peptide 401)	22	6	4	2×10^{-6}	143
ACTH (1–24)	24	7	4	3×10^{-6}	143
Protamine	32	21	6	3×10^{-7}	143
				2×10^{-8}	152
PTH (1–34)	34	5	3	10^{-6}	153

[a] ED_{50}s are estimates of the molar concentration at which the peptides released 50% of the maximum releasable histamine with that particular peptide.

[b] The multiphasic concentration-response curve prevents the assignment of meaningful ED_{50}.

critical distances between changed groups have not been measured with rigid probes. It is evident from Tables 2 and 3, and other studies, that nonbasic intervening residues must also contribute to activity. D. Lagunoff and H. Wan (unpublished), for instance, have found that a mixed polymer of tyrosine and lysine is twice as effective in releasing histamine as polylysine.

Polyarginine was found by Foreman & Lichtenstein (154) to be an extremely active, noncytotoxic histamine releaser when tested with human basophils with an ED_{50} of approximately 5×10^{-9}M. Polyornithine was even more active, but, as with rat mast cells, polylysine was less active. Polylysine, n=150, was significantly more active than a small polymer, n=15. It has been shown with polylysine applied to rat mast cells that when expressed on a g/ml basis, molecular weight does not affect releasing potency over a range of 3,000 to 70,000 (155). If the data were expressed in terms of molarity, the higher the molecular weight the more potent the polymer. This use of molarity based on total polymer size would be deceptive if the most active unit were, for example, 10 lysines in size, since larger polymers would then just represent strings of active units (n=10), and the critical aspect would be the equivalent molarity of active units rather than the actual polymer. Protamine, interestingly, was inactive with human basophils at concentrations as high as 5×10^{-6}M. Since relatively small polymers like polymyxin B and the 48/80 hexamer are so active, cross-linking of cell surface sites of any substantial size or separation is difficult to invoke. Very few binding studies with polybasic compounds have been performed (156), and it is necessary to bear in mind that artefacts can arise from binding of the releasing agents to negatively charged sites on exocytosed granules that remain associated with the cells. Evidence from experiments in which 48/80 (157) or polymyxin B (158) was attached to sepharose beads points to a site

Table 3 Polypeptide releasing agents

Polypeptide	Basic residues	ED_{50}[a]
Lysine	1	Inactive ($> 10 \times 10^{-3}$ M)
Dilysine	2	8.00×10^{-3} M
Trilysine	3	0.35×10^{-3} M
Tetralysine	4	$.055 \times 10^{-3}$ M
Arginine	1	Inactive (> 10 mM)
Triarginine	3	$.021 \times 10^{-3}$ M
Poly (Lys-Ala-Ala)	30	47.0×10^{-7} M
Poly (Arg-Ala-Ala)	15	3.5×10^{-7} M

[a] ED_{50}s are recalculated from data of Jasani et al (143).

of action of the polybasic compounds on the surface of the mast cell membrane.

Paucibasic Histamine Releasers

Numerous mono-, di-, and tribasic compounds including a number of widely used drugs cause histamine release from mast cells. If this activity is manifest at pharmacological concentrations, it can obviously be relevant in human therapy. Some of these agents cause histamine release by lysis or limited membrane damage; others induce noncytotoxic secretion. In most instances the mechanism has not been identified.

Criteria for cell lysis include a typical electron microscopic appearance, lack of dependence of release on cell ATP levels, activity at 4°C, persistence of the secretory process in cells heated to 50°C for 10–15 min, release of lactic dehydrogenase from the cells, and uptake of trypan blue by the cells. By the application of one or more of these criteria, stilbamidine (140, 159), morphine (159, 160), codeine (160), tubocurarine (140, 160), ketotifen (161, 162), and guanethidine (140), among the drugs tested, were demonstrated to act noncytotoxically. A basic dye, toluidine blue (159, 163, 164), also falls into this class. In contrast, pethidine (160), decylamine (140, 165), oxatomide (161), chlorpromazine (22, 140), and a number of antihistamines [G. Read and D. Lagunoff, unpublished, and (166)] are evidently cytolytic.

As Lorenz et al (87) have emphasized in their excellent review of the role of histamine in adverse drug reactions in humans, the results from studies on mast cells of experimental animals are not directly applicable to man, and a demonstration that histamine is released is not tantamount to proof that the adverse reactions are attributable to histamine release. We would add the caution that demonstration of a mechanism of action on animal mast cells does not establish the mechanism in man.

CALCIUM

A critical role for calcium ions was proposed early in the history of studies of histamine release, but the demonstration that elevation of cytoplasmic Ca^{2+} levels was sufficient to initiate the entire repertory of mast cell secretory activity had to await the introduction of calcium ionophores. Both A23187 (167–172) and ionomycin (173) have been clearly demonstrated in several available systems to release histamine by exocytosis, and a number of inhibitors of exocytosis, including some that decrease cell ATP and others that react with critical mast cell SH groups, interfere with ionophore-stimulated secretion. It would be going too far, however, to say that the ionophores are not cytotoxic; they are (169), but it is not their cytotoxicity that accounts for the histamine-releasing activity. Two other inventive means of directly elevating mast cell calcium and thereby stimulating hista-

mine secretion have been used: microinjection of calcium (174) and fusion of the cells with Ca^{2+}-loaded liposomes (175). Recent evidence (176) on the mode of action of one of the more surprising mast cell secretagogues, ATP, indicates that the mechanism is one of increasing cell Ca^{2+}, in this case by permeabilizing the mast cell membrane to small, charged molecules in general. It has not been possible to effect histamine release simply by raising the concentration of Ca^{2+} in the medium. Strontium ions (Sr^{2+}) and barium ions (Ba^{2+}), in contrast, will at 10 mM (177) and 30 mM (178) cause a slow release of histamine; release in the case of Sr^{2+} is sensitive to depression of cell ATP and can be blocked by Ca^{2+} (179).

OTHER COMPOUNDS THAT RELEASE HISTAMINE

There are a variety of agents and treatments of mast cells which do not readily fit into the classification we use in this review, and yet taken alone, none seems to require a separate category. We have taken the expedient of collecting them in this final section. Some of them, such as phosphatidic acid (180), low sodium (181), fluoride (182, 183), magnesium deficiency (184–186), and components of the complex drug solubilizer cremophor El (187, 188), may affect permeability of the mast cell membrane to calcium ions. Others, such as the chemotactic formyl methionine-containing peptides (189, 190), can be expected to operate through a highly specific receptor-mediated mechanism. Yet others, like haemacel (87), the cross-linked gelatin used as a plasma expander, require study in isolated cell systems to extend the information gathered from inadvertent and deliberate studies in intact humans and animals in order to categorize them. The one group of substances now included in this miscellany that may well require its own category is made up of the radiocontrast materials. The activity of these agents, which may be significant in humans, apparently is not dependent in a simple way on hyperosmolarity (191), although hyperosmolarity can release histamine from human basophils (192). In vitro studies using human basophils suggest that, in contrast to similar studies on rat mast cells (193), the radiocontrast materials are destructive of basophils and the mechanism may involve activation of the alternative complement pathway (191, 194).

It must always be remembered that many simple chemicals can act as antigens, and if, alone or as aggregates, they can induce or find appropriate IgE molecules on the mast cell or basophil surface, they can induce histamine release.

CONCLUSION

Mast cells are highly specialized secretory cells of the connective tissue. Together with the similarly active circulating basophils, they constitute a

system capable of responding to a wide range of foreign substances through multiple cellular mechanisms, activating a final common path that releases histamine, heparin, proteases, chemotactic factors, and other molecules. While in clinical medicine the effects of extreme and inappropriate histamine secretion are unwanted, it is probable that controlled release in many circumstances is a protective mechanism. It is surprising and disappointing that the information on the benefits of harboring the highly reactive mast cells and basophils is not more impressive than it is.

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