# PHARMACOLOGY AND FUNCTIONS OF THE MAST CELLS

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The mast cells have been the subject of numerous publications since they were first clearly described by the young Ehrlich (39, 40) some 75 years ago[1]; yet it is only comparatively recently that they have come to interest the pharmacologist. Modern work, particularly in Scandinavia and in Britain, has shown the functional activity of the mast cell in producing heparin (62) and histamine (106), and future work seems likely to be concerned with a further relationship of the mast cell to the connective tissues (104).

## I. MORPHOLOGY AND DISTRIBUTION

### *A. Blood and tissue mast cells*

There are two types of mast cell, both characterized by cytoplasmic granules with a strong affinity for basic dyes, some of which change colour (75) as staining occurs—metachromasia (39). The first and more common, *the tissue mast cell*, is found almost exclusively in the connective tissues (39). The second and rarer variety, *the blood mast cell* (basophil or mast leucocyte), takes origin in the bone marrow and with the other leucocytes enters the peripheral blood (41, 79, 80). It will be shown later that contrary to current belief (6, 82) these two types of mast cell have much in common.

### *B. Occurrence*

*1. Normal tissues.* Mast cells have been demonstrated at every level of the evolutionary scale, from invertebrates (26, 49, 69, 71, 124) through the lower vertebrates (15, 32, 34, 36, 48, 59, 81, 109) to the higher vertebrates (24, 30, 55, 119, 125, 129), including man (114). However, each species has its own particular pattern of distribution for which as yet there is no adequate explanation. Characteristically the cells are found in that loose fibrillary tissue (114), the so-called reticular tissue (35, 51), which surrounds small blood vessels (39, 99, 101) and underlies epithelial (24, 85), serous (106, 119) and synovial (4) membranes. Yet the dog has numerous mast cells in its liver parenchyma (55, 92), and the majority of the mast cells in the rabbit are in its blood (79, 125).

*2. Pathological tissues.* (a) *Inflammation.* Mast cells disappear locally in acute inflammation (39, 116) only to reappear with the onset of fibroplasia and repair (93, 114, 116). They increase still further in chronic inflammation (50, 58), especially when this is aggravated by chronic lymphatic obstruction (9, 125). It was this last observation which led Ehrlich (40) to choose the name 'Mastzellen' (well-fed cells) in the belief that the granules develop in certain connective tissue cells as a result of hypernutrition.

[1] Outstanding among the many interesting papers (8, 9, 45, 81, 112, 123) monographs (4, 16, 116, 125) and reviews (6, 17, 54, 55, 59, 67, 73, 80, 99, 104, 127) which have subsequently appeared, is the comprehensive survey by Michels (82).

(b) *Tumours*. There is a pronounced hyperplasia of the tissue mast cells during carcinogenesis in the skin of mice (27), and the cells often accumulate around established carcinomas in many species (125 and c.f. 27, 100). Certain tumours contain a high proportion of non-malignant mast cells (7, 35, 56, 117): very rarely the mast cells themselves give rise to malignant growths, such mastocytomas occurring most commonly in dogs (13, 91). Focal accumulations of mast cells are present in man in a variety of skin diseases (3), and especially in 'urticaria pigmentosa' (33, 118). Basophilic leukaemia has been reported but is extremely rare (31, 57).

### *C. The mast granules*

Mast cells do not contain mitochondria in the ordinary sense (24), but it is possible that the granules are 'giant mitochondria' (14, 104), an hypothesis which is in fact supported by their physical behavior (130) and histochemical properties (45, 86, 94). It is thus reasonable to suppose that the metachromatic material is synthesized (105), certainly concentrated (45), at these centres of enzymic activity. However, as Westphal (125) emphasized, the granules in many species are so soluble in water that the metachromatic material readily diffuses from the cell. Thus, the first prerequisite for the histological demonstration of mast cells in any species is adequate fixation (25, 36, 55, 80, 82, 98): the second is the use of a suitable basic and preferably metachromatic dye (39, 75, 82). In passing, it is worth noting that even well-fixed mast granules usually fail to stain with the most commonly used of all histological techniques, the haematoxylin-eosin method (27, 105).

## II. PHARMACOLOGY OF THE MAST CELLS

*1. The mast cell and heparin.* For details of the work which led to the discovery of heparin in the mast granules the reader is referred to the interesting monographs of Wilander (126) and Jorpes (62). Briefly, the Scandinavians had analysed heparin (so called from the high anticoagulant activity of extracts of dog liver) to the extent that it appeared to be a polymer of disaccharide units consisting of glucuronic acid and glucosamine. Jorpes then found that the ash was rich in sulphur and that heparin could be precipitated by, and was stained metachromatically with, toluidine blue (60). However, Charles and Scott (20), had already pointed out (p. 434) that even in the dog "the liver is not necessarily the seat of production for heparin, nor does it contain the only reserve of heparin in the body." Lison (75) then suggested that metachromatic staining of the tissues with toluidine blue is histochemically specific for high molecular polysulphuric acid esters. It was thence but a brief step to seek a metachromatic component of a tissue corresponding to its heparin yield. In this way Jorpes and his colleagues (55, 63) traced the heparin of the body to the mast cells, the only other metachromatic tissue commonly present, cartilage, having virtually no anticoagulant activity (61, 62). Here also appeared to be a teleologically satisfactory explanation of the perivascular location of the mast cells (39, 62, 99): and while we now perhaps have less confidence in the precise histochemical significance of meta-

chromatism (122, 128), later investigators have amply confirmed that the progressive increase in metachromasia which accompanies the maturation of the mast cell granules (101) does in fact constitute an index of the extent to which sulphation (5, 64, 65) has occurred and is a measure of the anticoagulant which can be derived from these cells (62). Thus high yields of heparin have been obtained from various human (38) and animal (62, 103) tissues rich in mast cells and from the isolated mast granules of mice (70). Exceptionally high heparin values are found in mast cell tumours from dogs (19, 95, 106). Heparin has also been demonstrated in mast leucocytes from a case of chronic myeloid leukaemia (78). As Jorpes (62) remarks (p. 62), "There is no doubt whatsoever about the nature of the granular substance of the mast cells. It is heparin".

*2. The mast cell and histamine.* Two considerations led the writer to suspect that histamine, as well as heparin, might be present in the mast cells. The first was the work begun last century on peptone shock in the dog; this has been reviewed from the historical standpoint by Wilander (126).

It is well known that intravenous injection of peptone into the dog produces a state of shock and incoagulability of the blood. The shock is a histamine shock and the coagulation defect is due to the entry of heparin into the blood stream (68): moreover, both the histamine and the heparin are released principally from the liver in this species (108). However, injection of histamine itself, while producing shock and swelling of the liver through spasm of the hepatic veins, does not release heparin (29), nor does the injection of heparin release histamine—pure heparin has an extremely low toxicity (62). This rather suggests that the peptone is acting at some common site in the liver from which both the heparin and the histamine are released: and since heparin comes from mast cells, of which there are plenty in the dog's liver (55, 92), it seemed reasonable to suppose that the histamine might also have its origin in the mast cells.

The second consideration concerns the skin disease urticaria pigmentosa, also first studied some 60 years ago (118). Histologically the lesion of urticaria pigmentosa is a 'benign mastocytoma', a focal collection of mast cells under a thin epidermis. Mild trauma to such a lesion is promptly followed by the localized appearance of the 'triple response' of Lewis (74), the classical sign of histamine release in the skin (28). Thus both the general release of histamine into the blood stream of the dog and the local release of histamine into the skin of the human subject with urticaria pigmentosa have this in common, that the 'shock organ' in each case is rich in mast cells.

Following preliminary investigation into the morphology and distribution of the mast cells in the normal rat (101), I carried out a series of experiments to see whether chemical histamine-liberators would react with the mast cells in this species (102). Briefly, it was found that the mast cells of the rat undergo disruption following the injection of histamine-liberators and that certain diamidines can actually be seen, by virtue of their fluorescence in ultra-violet light, to concentrate in the peritoneal mast cells prior to the disruption of these cells.

An excellent correlation was then found to exist between the mast cell contents and the histamine values of a wide variety of normal and pathological tissues

(106). Thus, comparison between embryonic organs containing few or no mast cells and the corresponding adult organs showed that only when the organs contain mast cells do they also contain histamine; and this association was even more evident when an adult organ was dissected into its component parts on the basis of the distribution of its mast cells and the parts were then assayed separately for histamine. Thus, ox liver capsule and ox pleura, which are exceptionally rich in mast cells, were found to have the highest histamine contents (200–300 μg/g) of all normal tissues studied (we have since found out how to obtain clean samples of ox liver capsule, with corresponding improvement in our previous figures for histamine in this tissue). West and I then tried the effect of raising the mast cell content of mouse skin by painting it repeatedly with a carcinogenic hydrocarbon, and of lowering the mast cell content of rat tissues by means of various histamine-liberators, and in every case we observed the same parallelism between the mast cell and the histamine content. The case for the mast cells as a source of histamine was finally clinched by our findings in a series of mast cell tumours, a mast cell 'tumour' from a child—more properly described perhaps as a large solitary lesion of urticaria pigmentosa—giving the unprecedented value for histamine of 950 μg/g (106); and we have since obtained values of this order in a series of mast cell tumours from dogs (19). Here also it was of interest to find that we could accurately predict the presence of tumour metastases in lymph nodes, spleen and liver on the basis of their raised histamine contents. To complete the story of the relationship of the mast cells to histamine we now have evidence from the work of Graham *et al.* (47) that much of the blood histamine also resides in the basophils, the mast leucocytes.

Thus it will be seen that investigation into the cytological location of histamine followed lines very similar to those which led to the location of heparin in the mast cells, and with like success.

## III. DISCUSSION

*1. Location of heparin and histamine in the mast cell.* If it is agreed that the evidence summarized above supports the view that much, though by no means all (44), of the heparin and histamine in the body is normally present in the mast cells, the question next arises of their precise location within the cell. The distribution of the metachromatism in vitally stained material certainly suggests that the heparin is in the granules (45), and Köksal (70) has now isolated mast granules from mouse connective tissue and has confirmed their anticoagulant activity. Recent work likewise indicates that the histamine also is in the granules. One might perhaps have suspected this from the finding that the fluorescent histamine-liberators appear first to become attached to particulate components of the cytoplasm of mast cells in the rat (102); and West and I have since observed that, when such cells undergo a reversible 'degranulation' following administration of a suitable dose of a histamine-liberator, it is only when the granules are disappearing that the histamine content of the tissue falls. 'Degranulated' mast cells may still be present in a tissue which has lost its histamine, 'regranulation' of the cells being associated with its return (43, 107). To settle

the question of the cytological location of the histamine West (unpublished data) used Köksal's method to obtain isolated granules from mice and found them to contain proportionately more histamine than any other fraction. Very recently a similar result has been reported by Mota *et al.* (88) for the mast granules of the rat. Hence it appears that both the heparin and the histamine are normally present in the *granules* of the mast cells.

*2. Heparin-histamine relationship in the granules.* Since heparin and histamine carry opposite charges it might be assumed that they coexist in the granules in the form of a salt—a 'heparinate of histamine'. While this might be so, the following facts suggest that the simple explanation is not entirely satisfactory: heparin and histamine show no tendency to recombine once they are in the blood; histamine is not a coagulant for heparinized blood, nor is heparin an effective antihistaminic; and the picture of peptone shock in the dog reveals that both histamine and heparin are exercising their own independent activity (68, 126). It might, of course, be argued that heparin, once released, has a greater affinity for its specific co-factor (complement) in the blood than it has for any histamine which may be present, and thus reunion is prevented, but Sylvén *et al.* (113) have already shown that heparin is united to its co-factor within the mast cell and is released as such. For the moment we may regard heparin and histamine in the granules as part of a more elaborate structure in which phospholipid, protein and possibly other components enter; this accords reasonably well with the known physical (14, 130) and chemical (66, 113) properties of the granules, their staining characteristics (84, 85, 94, 96) and their reaction to histamine-liberators (102, 106, 107).

*3. Release of histamine from mast cells.* In their classical paper on the chemical histamine-liberators MacIntosh and Paton (77) showed that histamine can be released from the tissues by many basic substances—diamines, diamidines, diguanidines etc.—all of which bear at least some structural resemblance to histamine itself. They thus suggested tentatively that these liberators release histamine by displacing it from its normal location in the tissues. However, while it may still be possible to stretch the hypothesis of MacIntosh and Paton to include the liberating action of the simplest of amines, ammonia (111), it can hardly apply to the comparable effect of sodium hydroxide; still less to that of tap water.

Some years ago I observed that when an electric current is passed between a pair of platinum electrodes placed on a fresh spread of rat mesentery moistened with saline, a wave of 'exploding' mast cells can be seen under the microscope to spread from the negative pole towards the centre of the field. These 'explosions' are caused by the liberation of sodium hydroxide at the cathode, an event which is soon followed by a fall in the histamine content of the disrupted area. In the intact animal intraperitoneal injection of sodium hydroxide releases the histamine into the peritoneal fluid. West and I investigated the ability of water to release histamine from small fragments of tissue in view of the instability in water of the mast granules in many species and found even water alone to be an efficient histamine-liberator. This has been turned to good account by Fawcett

(42, 43) who injected water intraperitoneally into rats until the peritoneal mast cells had disappeared; the further injection of the chemical histamine-liberator, compound 48/80,[2] then failed to release any histamine from the peritoneum, the source having been exhausted.

It seems, then, that in addition to the mechanism of histamine-release visualized by MacIntosh and Paton, simple hydration of the granules or hydration after mild saponification of phospholipid by alkali (46) can also release histamine from the mast cells. This again suggests that the histamine is held, preformed, in a loose complex in the granules and that it may be necessary to disturb only one component of this complex to permit the histamine to escape.

*4. Release of heparin from mast cells.* Heparin, along with histamine, is readily released into the blood stream of the dog; the blood becomes incoagulable and crystalline heparin has actually been recovered from such blood (62). This entry of anticoagulant into the dog's blood occurs in peptone shock (126), in anaphylactic shock (68) and in the shock which follows the injection of chemical histamine-liberators (77), both the heparin and the histamine being derived principally from the liver of this species (108).

Histologically these various shocks in the dog are characterized by degranulation and disruption of the numerous mast cells in the liver parenchyma (90, 115, 126), and it would seem reasonable to infer that the diffusion of metachromatic material from the mast cells which is seen under the microscope does, in fact, represent heparin on its way from cells to blood by way of the tissue fluids. In other animals the mast cells can be seen to undergo a similar disruption (102, 115), the histamine content of the tissue falls and again there is histological evidence of the escape of metachromatic material from the mast cells into the tissue spaces (107); but little or no anticoagulant can be demonstrated in their blood (1, 89). This is particularly characteristic of the rat (83) which carries an enormous population of perivascular mast cells in its connective tissues (101). On the other hand, the *extraction* of anticoagulant heparin from tissue is equally successful, whatever species of animal be used (20), and, although this demands proteolytic digestion and vigorous chemical manipulation (126), the final yield of heparin bears a direct relationship to the original mast cell content (55, 62, 63). The source of the heparin would thus seem to be the same in all species. The dog is unique in that active heparin appears in its blood.

One difference between the dog and other species is that its 'shock organ' is the liver (68, 126), and West and I recently have confirmed that much of the heparin and histamine released from the swollen liver reaches the dog's blood through its thoracic duct. It is probably not too much to say that had it not been for the obvious presence of heparin in the dog's blood in shock states, either heparin would not yet have been discovered or some other biological function would have been ascribed to it. For the moment we must leave it that the dog has its own particular way of handling the mast cell-heparin mechanism.

*5. The function of the eosinophil in the histamine problem.* For long the eosinophil was thought to be the chief source of histamine in the body (21). Recently,

[2] A polymeric condensation product of N-methylhomoanisylamine with formaldehyde.

however, the relation of the eosinophils to histamine has been found to be less close than was formerly supposed (22, 23, 37). Thus the highest histamine contents have been found by us in normal and abnormal tissues when the predominant cell was the mast cell (106), and when eosinophils appear in increasing numbers the histamine content is proportionately less. However, this occasional association of the eosinophil with the mast cell (23, 97) may itself indicate the true function of the eosinophil in the histamine problem.

In general, eosinophils are found in mast cell lesions when the mast cells are in course of disruption. Thus, eosinophils appear in the lesions of urticaria pigmentosa when these have been subjected to mechanical irritation (33), and we have recently observed the influx of eosinophils in a mast cell tumour taken from a dog treated with the histamine-liberator, compound 48/80. In the lungs of anaphylactically shocked guinea-pigs there is apparently developed some factor that draws eosinophils to the site (110). This factor may be histamine (120). It is, therefore, of particular interest that the isolated granules of eosinophils have recently been shown to possess *anti*-histaminic properties (121). Perhaps, therefore, we should regard the eosinophil as being concerned more with the detoxification and disposal of histamine than with its elaboration.

*6. Biological significance of mast cells in the organism.* (*a*) *Heparin.* From the time of Ehrlich onwards histologists have suggested that the function of the mast cell is concerned in some way with the connective tissue, and particularly with the formation of its fibrils (93, 99). This was forcibly expressed by Staemmler (114) who declared (p. 435) that 'the mast cells are unicellular glands of the connective tissues which, through their activity, elaborate the mucinous interfibrillary cement'. However, the formation of the first mast cells in the embryo (2, 72) is preceded by a general metachromatism of the tissues (52, 53). Thereafter, as mentioned above, the tissue mast cells undergo cyclic changes, disappearing in areas of acute tissue injury and reappearing when connective tissue fibrils begin to be laid down and the ground substance is shrinking (104). This behaviour on the part of the mast cells suggests that they alternately store (10, 18) and release (4, 116) the mucopolysaccharides of the ground substance; and since there is no doubt that the amino-sugar of heparin is glucosamine it is generally presumed that any polysaccharide of the ground substance derived from mast cells will also contain glucosamine. Asboe-Hansen (6), for example, regards the metachromatic substance of the granules as a sulphated precursor of hyaluronic acid. Purified heparin has also been used with some success to precipitate fibrils from solubilized collagen (87); and MacDougall (76) finds that the addition of mast cells to a tissue culture of fibroblasts favours the production of fibrils in the medium. However, these are no more than indications of what may ultimately develop into a subject of major importance, and further speculation on these lines at present is hardly profitable.

(*b*) *Histamine.* Histamine, too, may play some part in the normal organism (44), though it is apt to obtrude itself only in pathological conditions. In a recent study, West and I (107) noticed that the activation of the reticulo-endothelial system which follows histamine-release and which is manifest by an

increased phagocytic capacity of the endothelial cells (11, 12) is only part of a more widespread mobilization of the entire loose mesenchyme. This mobilization begins around the small vessels and extends away from them into the tissues. This led us to suggest that the changes in the mesenchymal cells might be due to a flooding of the tissues with protein-rich oedema fluid, formed as a result of increased vascular permeability (44). The general appearance of these activated cells closely resembles that seen in the inflammatory process; hence, we may infer that histamine liberated as a result of injury may play a similar part in that mobilization of the fixed tissue cells which precedes repair.

This review, then, covers two aspects of the 'riddle of the mast cells' (104). The first deals with the earlier studies on the mast cell and heparin and the newer work that relates the mast cell to histamine. The second attempts to correlate these various findings and suggests that the function of the mast cell in most species may be less concerned with blood clotting than with the maintenance and repair of the connective tissues. Whereas the pharmacology of the substances obtainable from mast cells—heparin and histamine—is now reasonably well established, the functional role of the mast cell in relation to the connective tissues has only begun to be studied.

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