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Interactions of Mast Cells with the Nervous System - Recent Advances*

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This article reviews recent advances in the understanding of mast cell-nervous system interactions. It is drawn largely from work published within the last ten years, and discusses the anatomical and biochemical evidence of a functional connection between mast cells and the nervous system, and the implications that such a relationship may have for normal and abnormal physiological functioning. Mast cells are found at varying levels of association with the nervous system; in CNS parenchyma (mainly thalamus), in connective tissue coverings (e.g. meninges, endoneurium), and in close apposition to peripheral nerve endings in a variety of tissues. There is, as yet, no clearly defined role for mast cells in nervous system function, or vice-versa, and it seems most likely that their interactions fulfil mutually modulatory roles. By extension, pathological situations where one of the partners in this relationship is overly stimulated may lead to a dysregulation of the other, and contribute to disease symptomatology.

KEY WORDS: Mast cells; nervous system; neuropeptides; neurotransmitters; demyelination; review.

Mast cells are granulocytic immune cells that are predominantly observed in perivascular locations in mucosal and serosal tissues. They are also resident within the normal nervous system, and are often observed in close apposition to neurons in a variety of peripheral tissues. In discussions of immune system-nervous system interactions, mast cells are often overlooked, even though their association with the nervous system has been known for over 100 years (1). The study of their possible interaction with the nervous system is an active area of investigation, and as will be described below, evidence is accumulating for mutual interactions between mast cells and the nervous system, which may have implications for the role of these systems in both normal and abnormal physiological situations.

Since there does not seem to be a single unifying feature of mast cell-nervous system interactions, this review will describe a variety of different aspects of this field. More comprehensive reviews of particular areas of study will be referenced where appropriate. In addition, this article is largely confined to a discussion of more recent advances in knowledge in mast cell-nervous system interactions, and is based on information obtained within the last decade. For reviews of earlier studies in this field, mainly concerned with anatomical identification and distribution of mast cells within the nervous system, the reader is referred to the detailed reports of Olsson, Ibrahim and Dropp (2–4). The present article is divided into three main sections; the anatomic

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Abbreviations: ACh, acetylcholine; BMMC, bone marrow-derived mast cells; CGRP, calcitonin gene-related peptide; EAE, experimental allergic encephalomyelitis; EAN, experimental allergic neuritis; 5-HT, serotonin; IgE, immunoglobulin E; IL-3, interleukin-3; MS, multiple sclerosis; NA, noradrenaline; NF, neurofibromatosis; NGF, nerve growth factor; VIP, vasoactive intestinal polypeptide.

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locations where mast cell-nervous system interactions may occur, the possible molecular bases of these interactions, and the potential significance they may have for health and disease.

MAST CELL BIOLOGY

This review is specifically concerned with mast cell-nervous system interactions, and more extensive discussions of recent advances in general mast cell biology are available elsewhere (5–8). In the last decade, there have been significant increases in the numbers of mediators reported to be released by mast cells, and in the type of stimuli capable of causing such release. In particular, there have been major advances in the understanding of how the tissue microenvironment can affect mast cell phenotype (9). Although mast cells are still generally defined as "connective tissue type" or "mucosal type", there is a potentially much wider range of heterogeneity in their morphology, response to different stimuli, and the qualitative and quantitative content of mediators that they can release. A particular phenotype may be influenced by both location, stage of development and immune activation. Mast cell contents may also differ between species. For example, serotonin, a significant component of rodent mast cell granules, is absent from mast cells of higher mammals. Figure 1 shows a generic mast cell, illustrating the wide range of stimuli for mast cells, and the numerous mediators they can release. The close association of such multipotent cells with the nervous system provides a significant opportunity for neuroimmune interactions.

ANATOMY OF MAST CELL-NERVOUS SYSTEM ASSOCIATIONS

Although mast cells have been observed in a variety of nervous system locations in different species, they appear to be concentrated in relatively few locations. Recent studies of mast cell-nervous system interactions have generally been conducted in rodents, and have been largely concerned with mast cells located within one of the three main areas where anatomic proximity makes some mutual interaction appear most likely. These locations have varying degrees of anatomic integration within the actual nervous system, and include (a) the diencephalic parenchyma (particularly the thalamus), (b) the connective tissue coverings of the nervous system (e.g., meninges, endoneurium), and (c) the tissues associated with the ganglia, neurons and nerve endings of the autonomic nervous system.

Diencephalon. Thalamic mast cells appear to represent the major population of parenchymal CNS mast cells in most species studied thus far (2-4). A detailed survey of the adult rat brain by Goldschmidt et al. (10) found greater than 98% of total brain mast cells were located in the thalamus of the adult rat, with the remainder in the parietal cortex, or near the optic chiasm. Within the thalamus, they were concentrated in the ventral, medial dorsal and ventral dorsal nuclei. Another report described mast cells in both the thalamus and hypothalamus of the rat (11).

Meninges. The connective tissue coverings of the nervous system are rich in mast cells (2-4). A recent study of mast cells at the surfaces of mouse CNS reported a similar distribution to previous studies, namely, a typical perivascular location, a preponderance of mast cells in the brain and spinal cord dura mater, spinal periosteum, the roof of the third ventricle and in the vicinity of spinal roots (12). Although mast cells in the rat dura are aligned with the meningeal artery, and the branches of the trigeminal nerve, they appear to be more closely associated with connective tissue elements (13). Interestingly, meningeal mast cells may themselves receive sympathetic innervation (14,15).

The presence of mast cells within the endoneurium, perineurium and epineurium of PNS fiber tracts has been known for some time (2), and there have been few recent studies of this population. Mast cells are located diffusely throughout the endoneurial sheath, and in Lewis rats are present at a density of about 7 cells per mm^2 (16–18).

Peripheral Nervous System. An active area of research in recent years has concerned possible connections between mast cells and nerves in peripheral tissues, particularly those receiving autonomic innervation. A number of morphological studies at both the light- and electron-microscopic level have reported mast cells located in close apposition to autonomic nerve endings in a variety of tissues including skin, gastrointestinal tract, respiratory tract, mesentery, diaphragm, thymus, and cerebral blood vessels (14,15,19-31). Although direct contacts between mast cells with nonmyelinated nerve endings have been reported, contacts via true synapses on mast cells have not been found (23,24,31). Co-cultures of mast cells and neurons may provide a means of examining the cellular basis for these interactions (32,33). While the anatomic proximity of mast cells and nerves does appear to be strong evidence of a functional connection, it should be noted that a detailed study of rat

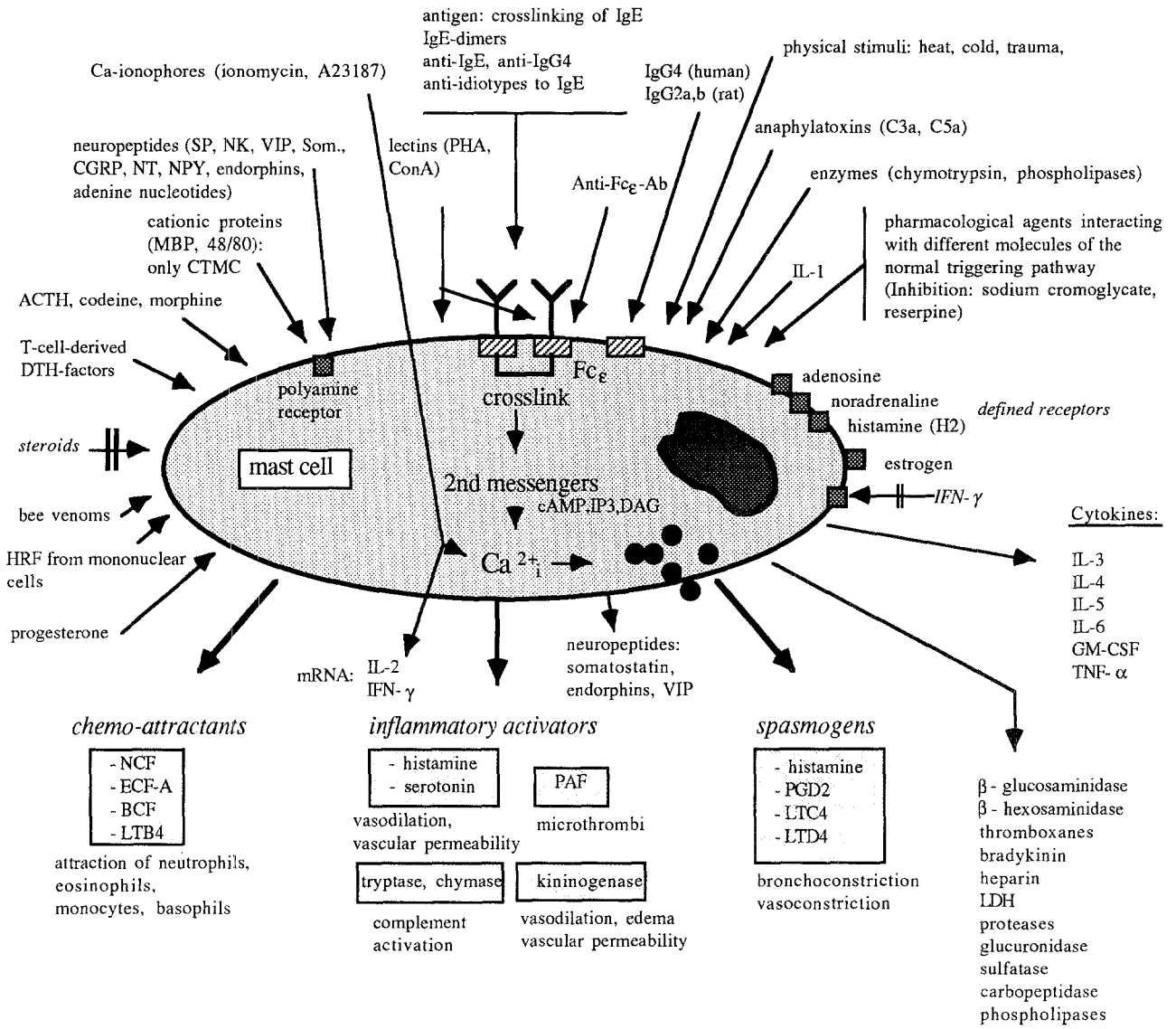

Fig. 1. *Generic mast cell.* This figure shows a composite mast cell derived largely from references 5-9, and is presented in this fashion to show the potential range of both stimuli and secretory responses of mast cells. It should be stressed that not all mast cells secrete all these mediators, and that not all mast cells respond to these stimuli. The exact phenotype of a particular mast cell is influenced largely by tissue location, developmental stage and immune activation.

Abbreviations used: adenocorticotropic hormone (ACTH); antibody (Ab); basophil chemotactic factor (BCF); calcitonin gene-related peptide (CGRP); concanavalin A (ConA); connective-tissue type mast cell (CTMC); delayed-type hypersensitivity (DTH); diacylglycerol (DAG); eosinophil chemotactic factor (ECF); high-affinity receptor for IgE ($Fc_\epsilon RI$); granulocyte-macrophage colony stimulating factor (GM-CSF); histamine releasing factor (HRF); immunoglobulin E (IgE); interferon (IFN); interleukin (IL); lactate dehydrogenase (LDH); leukotriene (LT); myelin basic protein (MBP); nerve growth factor (NGF); neurokinin (NK); neuropeptide Y (NPY); neurotensin (NT); neutrophil chemotactic factor (NCF); platelet activating factor (PAF); phytohemagglutinin (PHA); prostaglandin (PG); somatostatin (Som); substance P (SP); tumor necrosis factor (TNF); vasoactive intestinal peptide (VIP).

small intestine by Arizono and co-workers reported that, in addition to mast cell-nerve proximity, neural processes were similarly close to eosinophils and plasma cells, and they suggested that these associations may reflect a density of the various elements in the tissue studied (34). An understanding of the physiological significance of mast cell-nerve association requires additional functional studies, and some of these are reviewed below.

DEVELOPMENT

Immature mast cells can first be detected in the rat brain around embryonic day 17. They increase in number during the first ten days after birth, by which time their numbers are highest. At this stage they are predominantly observed in the diencephalic leptomeninges. Over the next few days, total mast cell numbers decline somewhat, and the remaining cells begin to migrate along blood vessels penetrating the brain parenchyma, particularly the thalamus (35-37). Between postnatal days 15 and 20, while total numbers of diencephalic mast cells remain constant, the proportion of them associated with thalamic parenchymal blood vessels increases from 20% to 90% (35). Once these mast cells have taken up their position within the thalamus they appear to develop into classical connective tissue type mast cells, increasing in size and changing their morphology. It is of interest that when mast cell-deficient adult W/W^v mice are reconstituted with bone marrow cells from normal littermates, mast cells colonize the thalamus in a similar pattern seen in normal adult controls (17), suggesting that the attraction of mast cells to the thalamic parenchyma is not absolutely linked to nervous system development. There is evidence that CNS mast cell number may be hormonally regulated during development; numbers of brain mast cells were decreased 30% by treatment of neonatal rats with thyroid hormone, while administration of an antithyroid agent caused a 30% increase (38).

There have been no detailed accounts of turnover of nervous system mast cells although studies of peripheral tissues suggest that if it occurs, it will be slow (39). Studies in our laboratory have shown that peripherally administered mast cell precursors from normal littermates can enter the adult CNS and PNS of W/W^v mice, suggesting that some turnover may be possible (17). In preliminary studies with interleukin 3-dependent bone marrow-derived mast cells (BMMC), we have found that a proportion of these cells can enter the nervous system of normal rats and mice from the periphery (Yasui, Krenger and Johnson, unpublished observations).

VARIATIONS IN NERVOUS SYSTEM MAST CELL NUMBER

Several studies of nervous system mast cell number have remarked on its variation between individual animals of the same strain, and between strains of the same species. Brain mast cell numbers may differ between sexes, and between left and right sides of the brain, in addition to some apparently random variation between individual animals (4,10). It is not clear what the mechanism(s) for these variations might be although Persinger (40) has reported that handling of rats from an early age has a significant effect on mast cell number, and there has also been a report of circadian rhythms in dural mast cells (41). There must be at least a degree of genetic control as consistent differences in mast cell numbers in both the CNS and PNS between different rodent strains can be observed (17,42). In addition, a number of other factors may influence mast cell number at a given location, including innervation, vascularization, or hormonal influences (38). It should be noted that despite variations in numbers of mast cells, their general distribution within the nervous system remains constant (10). W/W^v mice have no detectable mast cells in either the CNS or PNS (17,43).

PHENOTYPE

There has been much recent work on the effects of tissue microenvironment on mast cell phenotype (9). However, there have been few detailed studies of the phenotype of nervous system mast cells. Mast cells within the connective tissue coverings of the nervous system appear to be of the classical connective tissue phenotype (2-4,13). Although it has been suggested that there may be two populations of dural mast cells, based on morphological criteria (44), the observed differences in shape and size may be due to physical constraints imposed by different dural layers (13). The parenchymal mast cells of the thalamus also appear to largely resemble the connective tissue type, although they may have a significantly lower histamine content than do peritoneal mast cells, an increased lipid content, and different secretory patterns (10,11). The phenotype of mast cells associated with autonomic innervation is presumably influenced by the tissue in which they are resident. Mast cells in the developing brain have some characteristics of immature cells, and it has been suggested that they may be similar to mucosal type mast cells (37). Considering the high capacity of mast cells to modulate their phenotype in response to their tissue environment, it is likely that further modifications of nervous system mast cells will be described. One way to examine this question is by the use of co-culture systems of mast cells and nervous system cells. Mast cells form contacts with sympathetic neurons in vitro, although the effects of such contacts on mast cell phenotype have not been reported (32,33). As mast cells are in close proximity to glial cells in both the CNS and PNS, we have examined their interactions in vitro, using the protocol of Levi-Schaffer et al. (45).

We have successfully co-cultured rat peritoneal mast cells with astrocytes, and Schwann cells, for up to thirty days, and examined mast cell phenotype during this period. No changes in mast cell phenotype are apparent at this stage (46). Schwann cell conditioned medium can also support the development of mast cell progenitors (47).

Earlier reports that the CNS may contain a novel population of lipid-rich cells with mast cell-like properties ("neurolipomastocytes") (14,36,48,49) have recently been questioned (50). It remains to be convincingly demonstrated that these cells belong to the mast cell lineage.

REGULATION OF MAST CELL PHYSIOLOGY BY THE NERVOUS SYSTEM

There is now much evidence that elements of the nervous system can influence the growth, differentiation and, particularly, the activation state of mast cells. In recent years the actions of neurotransmitters and neuropeptides have been investigated predominantly in vitro on isolated mast cell preparations. Mast cells exhibit a range of responses to noradrenaline (NA) and acetylcholine (ACh) which seem to be dependent on the origin of the mast cell preparations and on the experimental system used. Noradrenaline stimulates histamine release (51), but in low concentrations in the presence of Compound 48/80, NA and other adrenergic agonists exert an inhibitory effect on histamine release (52,53). Similarly, the response of mast cells to acetylcholine is heterogeneous. Although this neurotransmitter has been reported to stimulate the release of histamine and monoamines from rat mast cells (54,55), there may be both responsive and non-responsive mast cell populations in the same species (56,57). Interestingly, sensitization of mast cells with antigen-specific immunoglobulin E (IgE) and antigen greatly increases the histamine release induced by ACh and renders the non-releasing population responsive to the neurotransmitter (57,58).

In recent years the major neuropeptides, among them substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal polypeptide (VIP), neurokinins, bradykinin, somatostatin, neurotensin, neuropeptide Y, opioid peptides and adenine nucleotides all have been reported to stimulate mast cells to release mediators either directly or via modulation of the response to other degranulating stimuli (59-75). Again, there is a wide range of site-specific and species-specific responses of different mast cell populations to these neuromodulators. The receptors and binding kinetics for some of these substances have been characterized on mast cells (76-81). Recent studies suggest that substance P, VIP, somatostatin and opiates may share a common activation pathway for secretion (82).

Although the in vivo significance of these various in vitro interactions is not clear, studies suggest that they may also occur in situ. The importance of mast cell-nerve interactions in physiological and pathophysiological conditions has been extensively investigated and reviewed (26,28,83-91) and we will therefore only briefly summarize the current knowledge. It is known that sympathetic and parasympathetic nerves can modulate the activation state of mast cells in the periphery (89). Stimulation of these autonomic fibers induces mast cells to degranulate and to release histamine and other mediators in respiratory and gastrointestinal tracts of humans and animals (92-95). Dependent on experimental conditions, exogenous sympathetic stimulation, during and after antigenic activation of mast cells in allergic laboratory animals, can downregulate contractile responses of respiratory smooth muscle by inhibiting rather than stimulating mast cell degranulation (96). In addition to autonomic fibers, neuropeptides released from activated cutaneous sensory fibers also induce mast cells to secrete histamine (97). Histamine in turn induces vasodilation and increased vascular permeability and may be involved in neurogenic inflammation (see below). An involvement of substance P and mast cells in peripheral vasogenic mechanisms has been suggested by the ability to inhibit vasodilation by antihistamine pretreatment (61,98).

Neuropeptides released by cutaneous sensory nerves have been shown to affect smooth muscles, blood vessels and leukocytes through the actions of mast cell mediators and the interaction of mast cells with nerves may thus be involved in hypersensitivity disorders such as immediate-type and delayed-type hypersensitivity reactions (99,100) and neurogenic inflammation.

Neuronal connections may also play a role in mast cell metabolism, as increased nerve activity can raise intracellular serotonin (5-HT) levels in meningeal mast cells, while denervation leads to a decrease in the content of this neurotransmitter (15). In the synovium, mast cell density parallels the extent of innervation (101). Interestingly, nerve growth factor (NGF), besides enhancing antigen-mediated histamine release (85) can affect mast cell development: the administration of NGF to cultured blood cells causes an increase in number and size of mast cells (102,103). Also, spleen cells pretreated with NGF and then injected into the brains of developing rats differentiate into mast cells (104). However, NGF in vitro does not appear to have an effect on the proliferation of interleukin 3-dependent BMMC (Johnson, Krenger and Dakin, unpublished observations).

As mentioned earlier, glial cells can support mast cell growth in vitro. Although the factors involved in this are not known, it is of interest that both astrocytes and Schwann cells have been reported to secrete NGF under certain conditions (105,106).

NEUROMODULATION BY MAST CELLS

The role of mast cells as mediators between immune and neuronal systems is supported by evidence that they seem not only to be influenced by the nervous system, but their mediators can in turn act on neurons. Histamine, for example, is a major neurotransmitter (107,108) released by activated mast cells by a variety of stimuli (Figure 1). Despite the controversy over its contribution to total CNS histamine (10,43,109-111), mast cell-derived histamine may be considered to be a major mediator between the mammalian immune system and the peripheral nervous system. In fact, mast cells are able to up- or down-regulate synaptic transmission (112-114) with histamine as the major effector and induce electrophysiological changes in vitro (32,115). As antigens can stimulate mast cell degranulation in isolated cervical ganglia (114) and an increased autonomic responsiveness has been found in atopic patients (116), it is possible that these mast cell-nerve interactions in the periphery play a role in certain allergic diseases such as bronchial asthma.

Rodent mast cells can also release 5-HT, another neurotransmitter, although as with histamine, the contribution of mast cells to total brain 5-HT is still unclear (117). Recently, an approach using in vitro perfusion of brain slices was applied to study the co-localization of 5-HT with mast cells in the brain: there is now evidence that rat brain mast cells can release 5-HT after activation with the secretagogue Compound 48/80 (118). Similarly, in peripheral ganglia, it has been possible to determine the contribution of mast cell-derived 5-HT to total 5-HT (119). It is conceivable that serotonin, like histamine, may be able to modulate neuronal function in the nervous system. In the periphery, serotonin derived from mast cells activated with Compound 48/80 may induce alterations of the myoelectric activity in the gastrointestinal tract (120). Further investigation will be necessary to assess the role of other potential neurotransmitters such as VIP and somatostatin-like molecules, which have been reported to be released by activated mast cells (121,122).

ROLE OF MAST CELL-NERVOUS SYSTEM INTERACTIONS

As is the case for mast cells in non-nervous tissues, their role in normal nervous system function is unclear. It is unlikely that they have any one particular role, and their function probably differs depending on their site of association with the nervous system. Their characteristic perivascular location, and vasoactive amine content, has led to speculation that they may be involved in regulation of cerebral blood flow or blood vessel permeability (3,10,11,123). While this is a reasonable hypothesis, we are unaware of any evidence that this is a routine phenomenon, and it is more likely to be operative in pathological situations, such as CNS infection, where there is a need to increase local blood vessel permeability. For example, when W/W^v mice were injected intracerebrally with Sindbis virus, the inflammatory response within the CNS, as measured by numbers of infiltrating cells, was reduced 50% compared to controls, suggesting a facilitatory role for mast cells in this case (124,125). Situations where this capacity to increase permeability across the blood-brain barrier may be detrimental, rather than protective, are discussed below.

The presence of large numbers of mast cells in the connective tissue coverings of the nervous system suggests that they may be serving a protective role. A major role of mast cells in the periphery appears to be in defense against parasites, such that infestation of the gut, for example, generally leads to mast cell hyperplasia (e.g 25,34). To our knowledge, however, there have been no reports of such a proliferation of mast cells in parasitic infestations of the brain. We recently examined brain tissue from several cases of neurocysticercosis, where the CNS is invaded by the larval stage of the cestode *Taenia solium.* Using a variety of mast cell stains, we did not observe any increase in brain mast cell numbers compared with controls (Nicolai, Toms and Johnson, unpublished observations). Another potential role for peripheral mast cells may relate to connective tissue formation in development or repair, and it has been suggested that this may also apply to dural mast cells (13).

The striking concentration of mast cells in the thalamus of many species suggests that they may have some functional significance. Although their presence may have arisen originally as a consequence of some unique feature of diencephalic innervation or vascularization, it seems possible that they would have assumed some regulatory function. The content of histamine and (in rodents) serotonin suggests that mast cells may function in control of local hemodynamics, and/or modulate thalamic activity through release of neuromodulators. The thalamus is

a major relay for afferent pathways, which may enable mast cells to exert some control on sensory processing. It is of note that differences in handling of rat pups appeared to have an effect on thalamic mast cell numbers (40). Although W/W^v mice appear grossly neurologically normal (except for seizures), it might be productive to examine them for more subtle defects stemming from a lack of thalamic mast cells.

Although the many descriptions of anatomic and functional connections between mast cells and peripheral neurons strongly support a physiological role for the mast cell-nerve interactions, the precise nature of this role remains undefined (90,91). As with other types of interactions between the nervous system and mast cells, their role in pathological situations may be more clear.

ROLE OF MAST CELL-NERVOUS SYSTEM INTERACTIONS IN DISEASE

There is evidence that increased activity at some level of the mast cell-nervous system axis may contribute to the symptomatology or pathogenesis of a variety of diseases. This involvement may be linked to activation of resident nervous system mast cells (inflammatory demyelinating disorders), mast cell hyperplasia (mastocytosis, neurofibromatosis) or reflect an overstimulation of a modulatory peripheral nerve-mast cell connection (neurogenic inflammation).

Inflammatory Demyelinating Disease. An association of mast cells with multiple sclerosis (MS) plaques, was first reported over 100 years ago (1). This observation has since been repeated several times, and mast cells have been observed in both active plaques and chronic "burnt out" regions of demyelination, where little active infiltration is evident (126-128). Although their presence in quiescent plaques may represent a secondary accumulation following the formation of scar tissue (129), mast cells at the site of an active lesion may contribute to lesion progression through the release of inflammatory mediators. It is of interest that submeningeal and periventricular regions of the CNS, which are particularly susceptible to inflammatory demyelination, are also sites of mast cell accumulation in the normal brain and spinal cord. The studies of Griffin et al. (124,125), described above, suggested that mast cells can play a significant role in the development of CNS inflammation.

A number of experimental studies have further implicated mast cells in the demyelination process. Isolated mast cells release myelinolytic proteases (130,131), and myelin proteins can stimulate mast cell degranulation (130). PNS mast cells degranulate early in the pathogenesis of experimental allergic neuritis (EAN), and this is associated with increased permeability of the blood nerve barrier, and infiltration of circulating inflammatory cells (16,132-134). The major animal model of CNS demyelination is experimental allergic encephalomyelitis (EAE), and Bo et al. have recently described increased degranulation of brain parenchymal mast cells in actively induced EAE in Lewis rats, although significant changes in mast cell numbers were not observed (135). Another study has reported a decrease in the number of detectable peripheral and parenchymal CNS mast cells in rat EAE, which the authors ascribed to increased degranulation (136). Interestingly, we have observed increased numbers of pial mast cells, some of which appear degranulated, in passively induced murine EAE (137). It is possible that this may be due to a migration of mast cells along parenchymal blood vessels, in the reverse direction to that observed in brain development (37). We have demonstrated that encephalitogenic T cells produce interleukin-3 (IL-3) (137), which is chemotactic for mast cells in vitro (138). Additionally, increased amounts of IL-3 may stimulate mast cell proliferation (5-8).

The degranulation of mast cells in EAE would presumably be associated with release of histamine, and it is of interest that susceptibility to EAE in mice has been linked to their response to vasoactive amines (139), and increased levels of histamine have been reported in the CNS of rats with EAE (140). As is the case with MS, the normal distribution of mouse CNS mast cells mirrors the regions of early lesion formation EAE (12), and this, together with their perivascular location, and high content of inflammatory mediators, make them attractive candidates for a role in experimental demyelination. However, while there is circumstantial evidence of mast cell activation in inflammatory demyelination, it is not known whether this is incidental to the disease process or plays some pivotal role in pathogenesis. As one approach to answering this question, experimental demyelinating diseases have been treated with mast cell stabilizing drugs (134, 141, 142). Although these drugs were successful in reducing the severity and incidence of disease, this is not a definitive proof of mast cell involvement, as the drugs may have been acting on a non-mast cell population (e.g. 143). A more definitive test of mast cell involvement, possibly using native and reconstituted W/W^v mice, is needed.

Mastocytosis. One disease where there appears to be a clearer link between neurological symptoms and mast cell dysfunction is systemic mastocytosis, a disorder characterized by an excessive accumulation of mast cells. Manifestations of the disease occur through a concomitant increase in mast cell-derived mediators. Some

patients develop neurological symptoms such as headaches, cognitive disturbances, chorea or peripheral neuropathy (144-146). We are unaware of any pathological studies of mastocytotic brains, and so it is not clear whether CNS signs are associated with increased numbers of brain mast cells, although some symptoms can be relieved with mast cell stabilizing drugs (144). Our studies of mast cell migration to the nervous system suggest that mast cells may be able to enter the normal CNS from the periphery, and it is possible that this may occur at an increased rate in mastocytosis.

Neurofibromatosis. Neurofibromatosis (NF) is characterized by the widespread occurrence of neurofibromas, complex tumours comprised largely of Schwann cells (147). Mast cells are also present in increased numbers (148,149), and the pruritus associated with periods of rapid tumour growth in NF suggests that these mast cells may be stimulated to release histamine (150). A recent study reported that treatment of NF with a mast cell stabilizing drug not only reduced pruritus, but also slowed tumour development (151). This suggests that mast cell activation may actually contribute to the development of neurofibromas. It is of interest that NGF, which can stimulate mast cells (see above), may be produced in increased amounts in NF (152).

Mast Cell-Peripheral Nerve Interactions in Disease. As discussed earlier, there is a variety of structural and physiological evidence for functional connections between mast cells and peripheral nerve endings. Although the normal role of these connections is unknown, it is assumed that they play some mutually modulatory role in the actions of the two systems. It follows that overstimulation of either mast cells or peripheral nerves could be of clinical significance. Neurogenic inflammation occurs when antidromic stimulation of cutaneous sensory nerves induces vasodilation and vascular permeability. This is of diagnostic importance (wheal and flare in the triple response), but may also contribute to the inflammatory component of a range of inflammatory diseases, including arthritis, asthma, conjunctivitis and rhinitis (153). The contribution of mast cells to neurogenic inflammation is controversial. If sensory neuron-mast cell units exist, activation of the neurons may lead to release of neuropeptides (particularly Substance P), which could stimulate mast cell degranulation leading to inflammatory changes (154). This idea has been challenged on the grounds of the relative anatomic locations of the inflammation and the mast cells, and the observation that neurogenic inflammation in W/W^v mice appears unimpaired (155,156). However it still seems possible that mast cells may be involved in amplification or modulation of this process. The perivascular location of mast cells, and their concentration in the dura, has also led to speculation that they may be involved in headache pathogenesis (157-159). Although mast cells do not appear to be necessary for neurogenic inflammation in the dura mater (160), there is evidence that mast cells adjacent to the sensory nerves of temporal blood vessels in headache patients are degranulated (161,162).

In the case of neurogenic inflammation, mast cell degranulation may be precipitated by neuronal activation. Mast cells are best known for their role in immediate hypersensitivity (allergic) reactions, and thus it is likely that nervous system-mast cell interactions may play a role in allergic symptomatology, and evidence for this being the case has been discussed recently (163-165). Experimentally, allergen challenge of superior cervical ganglia from sensitized guinea pigs leads to depolarization of ganglionic neurons (166), as does activation of peritoneal mast cells in co-culture with mouse neurons (33).

CONCLUSIONS

In conclusion, there is much evidence to support the idea of a neuroimmune interaction at the level of the mast cell. The function of nervous system-associated mast cells is not clear, although their predominantly perivascular location places them in an ideal location to regulate both local blood flow and vascular permeability, and to act as a route of communication between the nervous system and the circulation. In general, mast cells seem to play a modulatory, rather than obligatory, role in nervous system functions, and this appears to be the case for the reverse interaction. It is possible that mast cells initially arose as a ubiquitous population of protective cells, and that with evolution, they entered into some mutually regulatory relationship with adjacent regions of the nervous system. Although the functional significance of this relationship to normal physiology may be subtle, it may contribute to the symptomatology of pathological situations involving aberrant activation of either mast cells or the nervous system.

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