Graziottin A.
Mast cells and their role in sexual pain disorders
in: Goldstein A. Pukall C. Goldstein I. (Eds), Female Sexual Pain Disorders: Evaluation and Management, Blackwell Publishing 2009, p. 176-179

Mast cells and their role in sexual pain disorders

Alessandra Graziottin
Center of Gynecology and Medical Sexology, Milan, Italy

Introduction

Mast cells play a key role in many sexual pain disorders including interstitial cystitis (IC), provoked vestibulodynia (PVD), and endometriosis. Mast cells are ubiquitous, present in virtually all organs and vascularized tissue where they work to modulate the immune response. In addition, mast cells are present in, and recruited to, sites of inflammation, where they orchestrate key steps in the inflammatory response. Granules released by mast cells contain angiogenic, pro-inflammatory, and neurotrophic factors. These granules are heterogenous and different substances are released depending on the type, location, and timing of the damaging event or agent. When persistently up-regulated, mast cells maintain chronic in- flammation, leading to a shift between nociceptive and neuropathic pain. This chapter reviews the biochemical complexity of mast cells to illustrate their role in sexual pain disorders.

The Importance of Mast Cells

Although mast cells were discovered over 100 years ago, they still represent a “biological enigma” [1]. Mast cells possess a series of biochemical and functional properties that place them at the center of both the inflammatory and immune responses. Mast cells are activated by stimuli of “agonists” and released by means of degranulation, a wide array of biologically active mediators. These mediators can be synthesized at the time of the stimulus, or can be immediately released from storage vesicles called cytoplasmic granules [2, 3]. Mast cells are able to respond to a wide range of agonist stimuli, and to differentially release biochemical mediators [4]. It is this heterogeneity that enables mast cells to have a functional role in a wide range of problems including sexual pain disorders, ranging from inflammatory conditions (IC) to neuropathic pain syndromes (PVD) to fibrotic involutions (endometriosis) [5–8].

Mast cells contain, and selectively release, biochemicals that mediate the typical signs and symptoms of local in-flammation including erythema, edema, increased local temperature, pain, and functional impairment as first described by ancient Roman physicians in “rubor, tumor, calor, dolor, functio laesa”. These changes can be seen during a cystoscopic examination of a woman with IC or vulvoscopic (see Chapter 7) examination of a woman with PVD. Mast cells also contain “neurotrophins” that activate the nerve endings of pain fibers, inducing proliferation and growth toward the epidermis of the nerve terminals in the inflamed mucosa. These changes are the morphological correlates, respectively, ofhyperalgesia and allodynia. These alterations in pain perceptions are typical of sexual pain disorders including PVD, generalized vulvodynia (GVD), and IC.

The Morphology of Mast Cells

Selye was the first to describe the human mast cell as rounded elements with an oval nucleus and cytoplasm filled with spherical metachromatic granules, located in the dermis, adjacent to blood vessels, nerve endings, glandular ducts, and hair follicles. Historically, Toluidine blue and Giemsa stains were used to visualize mast cells microscopically [9, 10]. Unfortunately, these stain techniques inadequately demonstrated the presence of mast cells in inflamed tissue, but with newer immunostaining techniques (immunotryptase) mast cells are more easily seen. This increased visualization has yielded evidence of mast cell proliferation in the initial stages of several sexual pain disorders including PVD, IC, irritable bowel syndrome (IBS), and endometriosis. In later stages of these diseases, when the chronic inflammation has led to fibrosis, mast cells may almost disappear from the functionally deserted tissue.

Mast cells are currently divided into three groups based on their immunocytochemical characteristics [11, 12]. Specifically, there are mucosal mast cells containing only tryptase (mast cell T); connective tissue mast cells containing tryptase, chymase, carboxypeptidase, and cathepsinG (mast cell TC); and mast cells that can be found in several different tissues containing chymase and carboxypeptidase (mast cells C). Although dermal mast cells have traditionally been thought of as indigenous only to the dermis, mast cells have a migratory capacity and demonstrate extraordinary functional adaptation in response to disturbances of tissue homeostasis [2].

The density of mast cells in inflamed tissue changes over time. In tissue where there is an acute inflammatory response, the concentration of mast cells is high. As the inflammation becomes more chronic, the number of mast cells decreases and may even disappear late in the fibrotic process. However, as the density of mast cells decreases, there is an

increase in neuronal proliferation. At this late stage of the inflammatory process, neuropathic symptoms, such as spontaneous hyperalgesia, become prominent.

Functional Role of Mast Cells

Dermal mast cells, which are strategically located between vessels and nerves, are directly stimulated by immunological signals from cytokines, immunoglobulin E, complement fractions, and neuropeptides [2, 13–15]. These activated dermal mast cells play several crucial roles in mediating the inflammatory responses discussed below:

(a) Neurogenic inflammation: Neuropeptide nerve growth factor (NGF), calcitonin gene-related peptide (CGRP), and somatostatin are released by stimulated or damaged dermo-epidermal nerve endings. These neuropeptides activate local mast cells, causing degranulation [14]. In addition, physical, chemical, or mechanical stimuli also act to trigger mast cell degranulation [16, 17]. Once released from the mast cells, cytokines, growth factors, vasoactive amines, and proteolytic enzymes influence the surrounding cellular elements, thereby coordinating the biological response to tissue injury with both defensive and reparative effects.

(b) The mast cell–mediated vascular response: Mast cells that adhere to the walls of blood vessels are part of a vascular control system responsible for constantly monitoring microcirculatory homeostasis [18]. Through the release of vasoactive mediators such as histamine, protease, tumor necrosis factor (TNF), and metabolites of arachidonic acid, mast cells induce vasodilation and increase vascular permeability, leading to tissue edema and erythema [19, 20].

(c) The mast cell–directed inflammatory response: As the inflammatory process develops, mast cells play a crucial role in the recruitment of circulating leukocytes, neutrophils, basophils, and eosinophils to the area of injury [21]. Specifically, mast cells release TNF, leukotrienes, proteases, and cytokines (especially interleuken-8) that mediate leukocyte marginalization and migration [22]. These leukocytes, along with resident macrophages, perform specific defence functions including phagocytosis and debridement.

(d) The mastcell–mediated neurogenic response: Local innervation is influenced by the functional state of the mast cell [23]. Specifically, NGF released by mast cells causes a reduction in the nociceptive threshold. This is the key mechanism responsible for the hyperalgesia in sexual pain disorders [24–26].

(e) Mast cell–mediated neovascularization and reepithelialization: Mast cells coordinate neovascularization in injured tissue by influencing the regrowth potential of endothelial cells. Specifically, histamine, heparin, TNF, interleuken-6, interleuken-8, platelet derived growth factor, vascular endothelial derived growth factor, transforming growth factor-beta, and fibroblast growth factor represent the “angiogenic pool” rapidly released by activated mast cells by means of degranulation. This angiogenic pool modulates the various stages of new vessel formation [27–30]. In addition, mast cells also act to influence the re-epithelialization process by mediating keratinocyte migration and proliferation around the wound edges, leading to the formation of new epithelium [31, 32].

(f) Mast cells role in scarring: Mast cells play an essential role in initiating scar tissue formation by mediating the activity of fibroblasts. The mast cells release substances with specific fibroproliferative activity including histamine, interleuken-1, interleuken-4, NGF, tryptase, fibroblast growth factor, and transforming growth factor beta [33–38]. Therefore, mast cells possess the biological signals needed to stimulate chemotaxis, migration, phenotype differentiation, and biosynthetic activity of fibroblasts. In addition, there are gap junctions between fibroblasts and mast cells that enhance the functional synergy between these two cell types [27].

Clinical Significance of Mast Cells

As shown above, mast cells show extraordinary complexity and heterogeneity in the content of their granules. More importantly, they are able to selectivity release different granules depending on the stage of the inflammatory process, the site of tissue damage, and the response of the other cells participating to the inflammatory process. Disinhibition of the inflammatory process and/or persistence of inflammatory stimulimay alter the healing process, maintaining an up-regulation of the mast cell’s response. This intensifies neurogenic inflammation and tissue damage, with two major consequences. First, there is progressive functional and anatomic damage associated with prominent tissue scarring, exemplified by the natural history of endometriosis. Second, there is up-regulation of nerve pain, with morphological and functional changes. This may contribute to the shift from the typical inflammatory response as seen in “early” PVD where mast cells are significantly increased in the vestibular mucosa, to “late” PVD where there is increased density of C-afferent nociceptors in the vestibular mucosa. In these later stages, pain shifts from nociceptive pain towards neuropathic pain.

Conclusions

Understanding the role of mast cells in the pathophysiology of local inflammation is critical if physicians hope to move from symptomatic, late interventions in conditions such as PVD to etiologically based multimodal treatments. Mast cells play a significant role as the sophisticated directors of the immune and inflammatory response; they can influence a positive or negative outcome, according to genetic, local, and contextual factors. Physicians can change the natural history of many inflammatory conditions that lead to chronic and aggressive pain disorders if they consider the critical role of mast cells and intervene in two ways: by reducing *agonist* stimuli that cause mast cell up-regulation and damaging degranulation, and by testing/using drugs that may act as *antagonist* modulators of mast cells, thereby reducing the release of inflammatory and neurotrophic substances [39].

References

1) Ehrlich P. (1879) Beitrage zur Kenntnis der granulierten Bindegewebszellen und der eosinophilen leukocyten. Archiv für Anatomie und Physiologie 3, 166-69.

2) Galli SJ. (1993) New concepts about the mast cell. The New England Journal of Medicine 328, 257-65.

3) Bradding P. (1996) Human mast cell cytokines. Clinical and Experimental Allergy 26, 13-19.

4) Theoharides C, Kempuraj D, Tagen M, Conti P, Kalogeromitros D. (2007) Differential release of mast cell mediators and the pathogenesis of inflammation. Immunological Reviews 217, 65-78.

5) Letourneau R, Sant GR, el-Mansoury M, Theoharides TC (1992) Activation of bladder mast cells in interstitial cystitis. International Journal of Tissue Reactions 14, 307-12.

6) Bornstein J, Goldschmid N, Sabo E. (2004) Hyperinnervation and mast cell activation may be used as histopathologic diagnostic criteria for vulvar vestibulitis. Gynecologic & Obstetric Investigation 58, 171-78.

7) Bornstein J, Cohen Y, Zarfati D, Sela S, Ophir E. (2008) Involvement of heparanase in the pathogenesis of localized vulvodynia. International Journal of Gynecological Pathology 27, 136-41.

8) Sugamata M, Ihara T, Uchiide I. (2005) Increase of activated mast cells in human endometriosis. American Journal of Reproductive Immunology 53, 120-25.

9) Enerback L. (1996) Mast cells in rat gastrointestinal mucosa. I. Effects of fixation. Acta Pathologica Microbiologica Scandinavica 66, 289-302.

10) Enerback L. (1996) Mast cells in rat gastrointestinal mucosa. II. Dye-binding and metachromatic properties. Acta Pathologica Microbiologica Scandinavica 66, 303-12.

11) Benyon RC, Lowman MA, Church MK. (1987) Human skin mast cells: their dispersion, purification, and secretory characterization. Journal of Immunology 138, 861-68.

12) Bienenstock J, Befus AD, Demburg JA. (1986) Mast cell heterogeneity. In: Befus AD, Bienenstock J, Demburg JA. (eds.) Mast Cell Differentiation and Heterogeneity. Raven Press,New York, pp. 391-402.

13) Bienenstock J,MacQueen G, Sestini P,Marshall JS, Stead RH, Perdue MH. (1991) Mast cell/nerve interactions in vitro and in vivo. American Review of Respiratory Diseases 143, S55-S58.

14) Williams RM, Bienenstock J, Stead RH. (1995) Mast cells: the neuroimmune connection. Chemical Immunology 61, 208-35.

15) Beaven MA, Baumgartner RA. (1996) Downstream signals initiated in mast cells by FceRI and other receptors. Current Opinion in Immunology 8, 766-72.

16) El Sayed SO, Dyson M. (1993) Responses of dermal mast cells to injury. Journal of Anatomy 182, 369-76.

17) Malaviya R, Morrison AR, Pentland AP. (1996) Histamine in human epidermal cells is induced by ultraviolet light injury. Journal of Investigative Dermatology 106, 785-89.

18) Waltner-Romen M, Falkensammer G, Rabl W, Wick G. (1998) A previously unrecognized site of local accumulation of mononuclear cells: the vascular-associated lymphoid tissue. The Journal of Histochemistry & Cytochemistry 46, 1347-50.

19) Valent P, Sillaber C, Baghestanian M, et al. (1998) What have mast cells to do with edema formation, the consecutive repair and fibrinolysis? International Archives on Allergy and Applied Immunology 115, 2-8.

20) Huang C, Sali A, Stevens RL. (1998) Regulation and function of mast cell proteases in inflammation. Journal of Clinical Immunology 18, 169-83.

21) Kanwar S, Kubes P. (1994) Ischemia/reperfusion-induced granulocyte influx is a multistep process mediated by mast cells. Microcirculation 1, 175-82.

22) Ribeiro RA, Souza-Filho M, Souza M,et al. (1997) Role of resident mast cells and macrophages in the neutrophil migration induced by LTB4, fMLP, and C5a. International Archives on Allergy and Applied Immunology 112, 27-35.

23) Schaffer M, Beiter T, Dieter Becker H, Hunt TK (1998) Neuropeptides: mediators of inflammation and tissue repair? Archives of Surgery 133, 1107-16.

24) Leon A, Buriani A, Dal Toso R, et al. (1994) Mast cells synthesize, store, and release nerve growth factor. Proceedings of the National Academy of Sciences 91, 3739-43.

25) Lewin GR, Rueff A, Mendell LM. (1994) Peripheral and central mechanisms of NGF-induced hyperalgesia. European Journal of Neuroscience 6, 1903-12.

26) Tal M, Liberman R. (1997) Local injection of nerve growth factor (NGF) triggers degranulation of mast cells in rat paw. Neuroscience Letters 221, 129-32.

27) Metcalfe DD, Baram D, Mekori YA. (1997) Mast cells. Physiological Reviews 77, 1033-79.

28) Levi-Schaffer F, Kupietzky A. (1990) Mast cells enhance migration and proliferation offibroblasts into aninvitrowound. Experimental Cell Research 188, 42-49.

29) Katayama I, Yokozeki H, Nishioka K. (1992) Mast cell–derived mediators induce epidermal cell proliferation: clue for lichenified skin lesion formation in atopic dermatitis. International Archives on Allergy and Applied Immunology 98, 410-14.

30) Nicosia RF, Bonnano E, Smith M. (1993) Fibronectin promotes the elongation of microvessels during angiogenesis in vitro. Journal of Cellular Physiology 154, 654-61.

31) Clark RAF. (1993) Biology of dermal wound repair. Dermatologic Clinics 11, 647-66.

32) Woodley DT, Chen JD, Kim JP, et al. Re-epithelialization: human keratinocyte locomotion. Dermatologic Clinics 11, 641-46.

33) Russell JD, Russell SB, Trupin KM. (1977) The effect of histamine on the growth of cultured fibroblasts isolated from normal and keloid tissue Journal of Cellular Physiology 93, 389-94.

34) Kupietzky A, Levi-Schaffer F. (1996) The role of mast cell-derived histamine in the closure of an in vitro wound. Inflammation Research 45, 176-80.

35) Kovacs EJ. (1991) Fibrogenic cytokines: the role of immune mediators in the development of scar tissue. Immunology Today 12, 17-23.

36) Gruber BL, Kew RR, Jelaska A, et al. (1997) Human mast cells activate fibroblasts. Tryptase is a fibrogenic factor stimulating collagen messenger ribonucleic acid synthesis and fibroblast chemotaxis. The Journal of Immunology 158, 2310-17.

37) Bressler RB, Lesko J, Jones ML, et al. (1997) Production of IL-5 and granulocyte–macrophage colony-stimulating factor by naive human mast cells activated by high-affinity IgE receptor ligation. Journal of Allergy and Clinical Immunology 99, 508-14.

38) Qu Z, Kayton RJ, Ahmadi P, et al. (1998) Ultrastructural immunolocalization of basic fibroblast growth factor in mast cell secretory granules: morphological evidence for bFGF release through degranulation. The Journal of Histochemistry and Cytochemistry 46, 1119-28.

39) D'Cruz OJ, Uckun FM. (2007) Targeting mast cells in endometriosis with janus kinase 3 inhibitor, JANEX-1. American Journal of Reproductive Immunology 58, 75-97.