Genitourinary mast cells and survival

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Abstract: Mast cells (MCs) are ubiquitous in the body, but they have historically been associated with allergies, and most recently with regulation of immunity and inflammation. However, it remains a puzzle why so many MCs are located in the diencephalon, which regulates emotions and in the genitourinary tract, including the bladder, prostate, penis, vagina and uterus that hardly ever get allergic reactions. A number of papers have reported that MCs have estrogen, gonadotropin and corticotropin-releasing hormone (CRH) receptors. Moreover, animal experiments have shown that diencephalic MCs increase in number during courting in doves. We had reported that allergic stimulation of nasal MCs leads to hypothalamic-pituitary-adrenal (HPA) activation. Interestingly, anecdotal information indicates that female patients with mastocytosis or mast cell activation syndrome may have increased libido. Preliminary evidence also suggests that MCs may have olfactory receptors. MCs may, therefore, have been retained phylogenetically not only to “smell danger”, but to promote survival and procreation.

Keywords: Arousal; cervix; contractions; mast cells (MCs); prostate; uterus

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Introduction

Mast cells (MCs) develop from hematopoietic precursors in response to stem cell factor (SCF) the ligand of the CD117 (KIT) tyrosine kinase receptor. Precursors then migrate from the blood into all tissues where they acquire their tissue-specific phenotype, influenced by the local microenvironment (1).

MCs are best known for causing allergic reactions when activated through exposure to an antigen (allergen) that crosslinks allergen-specific immunoglobulin E (IgE), already bound to the high affinity Fc epsilon receptor 1 (FceRI) (2). MCs can also be activated by anaphylatoxins (C3a, C5a), hormones, physical stimuli (pressure and temperature changes), as well as cytokines and neuropeptides (3) such as corticotropin-releasing hormone (CRH), neurtensin (4), and substance P (SP) (5). MCs express receptors for diverse ligands (6), including toll-like receptors (7) that can be activated by bacterial and viral products (8). MC stimulation can be enhanced by SCF and IL-33 (9), which together with SP, induce vascular endothelial growth factor (VEGF) release (5) and act as “sensors of cell injury” (10). Each MC contains about 500,000 secretory granules filled with numerous biologically active molecules (11).

MC stimulation leads to secretion of numerous vasoactive, muscle contracting, neurosenzitizing and proinflammatory mediators (3,12). In particular, histamine causes muscle concentration, exocrine gland secretion and vasodilation; it also activates the hypothalamic-pituitary adrenal (HPA) axis (13), as does MC-derived IL-6 (14) and CRH (15). In fact, MCs have been implicated in the regulation of HPA axis both in the brain (16), and its equivalent in the skin (17,18).

MCs can secrete the content of individual granules (19)
or individual mediators, such as serotonin, selectively without
degranulation (20). MCs can also communicate with neurons
by transgranulation (21) or undergo “polarized” exocytosis of
proteolytic enzymes at surface sites called “antibody-dependent
degranulation synapse” (22). MCs can also secrete nanovesicles
(exosomes) (23) containing many different biologically
active molecules (24), in a manner that may be guided by
antigens embedded in their phospholipid envelope (25).
Such exosomes could participate in immune (26,27) and
neuropsychiatric diseases (28,29).

The ability of MCs to secrete some mediators selectively (30),
permits MCs to participate in diverse processes without causing
allergic or inflammatory reactions (12). For instance, we showed
that IL-1 can stimulate selective release of IL-6 (31) and so
did SCF (32). We also showed that CRH stimulated selective
release of VEGF (33) and so did prostaglandin D₂ (PGD₂) (34),
all without any degranulation. Taken together, available data
suggest that MCs are capable of releasing a panoply of molecules
that may participate in many pathophysiological processes
such as innate immunity (1,35), autoimmunity (36), and
neuroinflammation (37), but may also have immunomodulatory (38)
functions.

**Effect of stress**

Emotional stress is the most common trigger of symptoms
in patients with systemic mastocytosis, characterized by
increased number and degree of activation of MCs (39).
In one case, symptoms worsened with stress and there was
an elevated serum CRH levels, with bone marrow MCs express
CRHR-1 (40). MCs (15) and other immune cells (41) can
produce CRH (42). Amazingly, even corticosterone has
been localized inside MC secretory granules (43).

It is not well understood how animals “smell danger”
or are attracted to their mates through odors since
the olfactory nerve does not connect directly to the
hypothalamus. We and others reported that stimulation of
nasal MCs leads to activation of the HPA (44-46) driving
the organism into a fight-or-flight mode. Recently olfactory
and taste receptors were identified in subpopulations of
human circulating leukocytes (47). MCs may turn out to
also express such receptors since brain MCs were reported
to be influenced by chemosensory cues associated with
estrus induction (48).

Surprisingly, MC numbers and reactivity have been
reported to undergo daily rhythmic variations (49) and the
reactivity of individual MCs was further shown to follow a
“circadian clock” (50,51). In this context, it is of interest
that mast cell behavior is affected by the pineal through
the expression of melatonin receptors and MCs release
melatonin, themselves (52).

Excessive stress can lead to pathological outcomes in
various tissues (53). Stress has been reported to induce
inflammatory change in rat bladders (54), as well as selective
release of VEGF (55), effects that are absent in MC deficient
mice (56). Acute stress (57,58) and locally secreted CRH (59)
activated MCs (53,59) leading to neurogenic inflammation
with subsequent chronic nerve sensitization (60).

MCs (15), immune cells (41), human endometrium,
intruterine pregnancy tissues (61,62), and local nerve
endings (42) can produce CRH (42). We reported high levels
of CRH and tryptase in products of conception from women
with habitual spontaneous abortions (63). Maternal stress has
been also linked to preterm delivery (64) and high levels of
CRH expression has been reported for placenta, decidua
and fetal membranes, where it induces prostaglandin
production and promotes labor (65). The decidua of women
with high levels of stress have also been reported to have
high number of tryptase-positive MC (66), as also reported
in aborted deciduals (67). Endometriosis tissue has also been
associated with high number of activated MCs (68), which
were shown to be increased in response to stress which
exacerbated endometriosis in a rat model (69).

**Genitourinary MCs**

MCs are present in animal and human bladder (70,71),
prostate (72-75), uterus (76-79), penis (80,81), vagina
(76,82) and placenta (83). However, their role in these
tissues is unknown especially since they are not known
to undergo allergic reactions. Uterine MCs are increased
during pregnancy and may be important for reproductive
processes (84,85). MCs can release muscle contracting
and vasodilatory substances that could contribute to
clitoral enlargement and uterine contractions (78,86,87).
IgE-independent MC activation has been reported to
augment contractility of guinea pig (88), mouse (89) and
human (86) myometrium. Activation of MCs also leads to
angiogenesis in the rat uterine cervix during pregnancy (90).
MC degranulation also modulates cervical contractility as
shown in the guinea pig (91).

Current evidence from clinical and laboratory studies
confirms that MC play a central role in the pathophysiology
of bladder pain syndrome/interstitial cystitis (BPS/IC)
(92,93) and possibly prostate hyperplasia (74) and sterile
prostate inflammation (73). Damaged or dysfunctional
urothelial cells produce cytokines, such as SCF, that can stimulate proliferation and/or activation of MCs (71). In fact, MCs are increased in the detrusor of BPS/IC (71,94-97), and are maximally activated by SCF (98,99) and nerve growth factor (NGF), which is increased in patients with BPS/IC (100). We have shown that CRH activates rat bladder MCs (101) and CRH is involved in signaling in feline bladder urothelial cells (102). In fact, CRH has been considered a mediator of emotional influences on bladder function (103).

**Effect of sex hormones**

Human MCs express estrogen receptors (104) activation of which increase MC stimulation (105,106). Estradiol also induced MC migration into the uterus and their degranulation (107). Treatment of mice with leutinizing hormone (LH), follicle stimulating hormone (FSH) or estradiol increased the number and extent of MC degranulation in the ovaries (108). Estrogen receptors are also expressed on bladder (109-111), and lung (112,113) MCs. Human MCs also express progesterone (114,115) and testosterone (116) receptors, but their activation appears to have an inhibitory effect.

One laboratory has reported gonadotropin-releasing hormone-like immunoreactive MCs in the habenula of doves (equivalent to the hypothalamic infundibulum in humans) (117), which increased during courting (118). MCs in ovarian, uterine and brain tissues change their histamine content throughout the rat estrus cycle; moreover, MCs are absent from the thalamus during pro-estrus but are present in the hypothalamus only during the estrus phase (119).

MC-derived mediators, especially histamine, are considered to be important in sexual arousal and coitus (120). Anecdotal information suggests that patients with mastocytosis or MC activation (3) may have increased libido. Uterine MCs were shown to have oxytocin receptors, activation of which prevented serotonin uptake and increased serotonin availability (121) that may positively affect sexual behavior. Circulating levels of oxytocin are known to increase during sexual arousal and orgasm in both men and women (122). It is interesting that intranasal oxytocin was reported to increase libido and related sexual behavior in a male subject (123).

**Conclusions**

MCs have been retained throughout the phylogenetic tree (124). Moreover, MC ability to produce numerous hormonal, immune and neural substances resemble that of the unicellular organism Tetrahymena dating from some 500 million years ago (125,126). MCs are present in all mammals and may be necessary for survival of the species by regulating immunity (127), protecting the organism against external triggers (53), supporting pregnancy (128), augmenting delivery and also ensuring optimal conditions for procreation.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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