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Role of female sex hormones, estradiol and progesterone, in mast cell behavior

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Female sex hormones have long been suspected to have an effect on mast cell (MC) behavior. This assumption is based on the expression of hormone receptors in MCs as well as on the fact that many MC-related pathophysiological alterations have a different prevalence in females than in males. Further, serum IgE levels are much higher in allergic female mice compared to male mice. Ovariectomized rats developed less airway inflammation compared to sham controls. Following estrogen replacement ovariectomized rats re-established airway inflammation levels' found in intact females. In humans, a much higher asthma prevalence was found in women at reproductive age as compared to men. Serum levels of estradiol and progesterone have been directly correlated with the clinical and functional features of asthma. Around 30–40% of women who have asthma experienced worsening of their symptoms during the perimenstrual phase, the so-called perimenstrual asthma. Postmenopausal women receiving hormone replacement therapy have an increased risk of new onset of asthma. Beside, estrus cycle dependent changes on female sex hormones are related to changes on MC number in mouse uterine tissue and estradiol and progesterone were shown to induce uterine MC maturation and degranulation. We will discuss here the currently available information concerning the role of these female sex hormones on MC behavior.

Keywords: degranulation, estradiol, mast cells, progesterone, uterus

INTRODUCTION

Mast cells (MCs) belong to the innate-compartment of the immune system and are widely known for their role in allergic reactions via their binding to IgE receptor (Alvarez-Errico et al., 2009). MCs are a common cellular component of both connective and mucosal tissues (Kitamura and Ito, 2005). Beside this, MCs contain a wide range of biologically active molecules, including biogenic amines, heparin or heparan sulfate proteoglycans, neutral proteases, and neuropeptides. In addition, upon stimulation, they also produce and eject a large number of factors (Wilhelm et al., 2000). Taking these characteristics together, it is clear that even a small number of such potent unicellular glands have a significant effect on different physiological processes.

In addition to the very well known and described mechanism of MC activation and posterior degranulation throughout IgE receptor, several other alternative but not redundant mechanisms of MC activation have been described (Mousli et al., 1994; Bradding, 2005; Kim et al., 2008). Among others, female sex hormones, estradiol and progesterone, have been proposed to activate MC (Chancey et al., 2005; Vasiadi et al., 2006; Narita et al., 2007; Zaitsu et al., 2007; Jensen et al., 2010; Jing et al., 2011; Walter et al., 2011). We will discuss in this review the current bibliography evidences about the effect of female sex hormones on MC functionality.

MAST CELLS EXPRESS ESTRADIOL AND PROGESTERONE RECEPTORS AND FURTHER RESPOND TO THESE HORMONES

Female sex steroid hormones act primarily via their receptors: estrogen via estrogen receptor ERα or ERβ, progesterone via progesterone receptor PR-A or PR-B (Carey et al., 2007). Steroid receptors are best described as nuclear receptors acting as transcription factors on gene expression. However, in the past decade abundant evidences accumulated showing addition binding sides localized at the plasma membrane (Levin, 2011), whose activation is more often involved in the rapid effects of steroids occurring within seconds to minutes (Watson et al., 1999; Watson and Gametchu, 2003). In this regard, it has been shown that classical ERα at the membrane but not in the nucleus mediates 17β-estradiol (E2)-induced rapid signaling to kinase activation (Levin, 2011). Similarly, extra-nuclear PR induces activation of ERK/MAPK kinases, which lead to cell surviving as well as cells migration (Levin, 2011). We and other authors have demonstrated the expression of, estradiol and progesterone receptors in human, mouse, and rat MCs (Theoharides et al., 1993; Chancey et al., 2005; Pang et al., 1995; Narita et al., 2007; Zaitsu et al., 2007; Jensen et al., 2010; Jing et al., 2011). Zaitsu et al. (2007) have shown mRNA expression of ERα but not ERβ in human and mouse MCs. Alongside the authors have also shown that E2 rapidly stimulated MC degranulation which could be blocked by tamoxifen, a tissue specific ER antagonist, clearly indicating that

estradiol-induced MC degranulation throughout one of its receptors. Bone marrow-derived MCs (BMMCs) isolated from ERα knockout animals did not degranulate in response to E2 treatment confirming that the E2 effect on MCs is more likely mediated by the ERα (Zaitsu et al., 2007). Due to the rapid onset of E2 effect on MC activation the authors concluded that E2 in this context does not function through the classical (genomic) mechanisms, which require enhanced mRNA and protein synthesis over 2 h or longer period and proposed that the effect is mediated by a membrane-associated (non-genomic) form of ER (Zaitsu et al., 2007). We were additionally able to show that the human mast cell line (HMC-1) treated *in vitro* with physiological concentration of E2 and P4 significantly increased the synthesis of β-tryptase, which is a serine proteinase abundantly produced by MCs, and is a marker of MC maturation. Beside, E2 and P4 treatment induced degranulation of HMC-1 *in vitro* (Jensen et al., 2010).

Supporting the idea of female sex hormones having an effect on MC function, Kirmaz et al. (2004) have demonstrated that allergen skin prick tests (SPT), a very sensitive and specific tests to detect allergic sensitization in atopic patients, is altered in women upon hormonal changes during the menstrual cycle.

In addition to female sex hormone receptor expression, MCs have been also shown to express androgen receptor (Chen et al., 2010). However, testosterone treatment had no effect on MC degranulation (Chen et al., 2010).

INFLUENCE OF ESTRADIOL AND PROGESTERONE ON MC FUNCTION: DO THESE HORMONES PLAY A ROLE IN MC-RELATED DISEASES?

The idea that female sex hormones, E2 and P4, may affect MC functionality and therefore have an influence on the symptoms of MC-associated disorders has long been suggested. Asthma and other allergic diseases of the airway are up to three times more common in women than in men during the early to middle adulthood and remains so through the reproductive years (De Marco et al., 2002; Mannino et al., 2002; Schatz and Camargo, 2003). A number of clinical and epidemiological studies suggested that female sex hormones are accountable for these differences. Beside this, postmenopausal women taken hormone replacement therapy had higher risk of new onset of asthma (Barr et al., 2004). Furthermore, 30–40% of women who had asthma, experience a worsening of their symptoms during the perimenstrual phase of the menstrual cycle (perimenstrual asthma) being the time point when E2 and P4 concentrations are changing rapidly (Vrieze et al., 2003). In this context, it is of great importance to mention that the prevalence and morbidity of asthma and other allergic diseases have increased dramatically during the last 30 years, particularly in developing countries (Burr et al., 2006). Narita et al. (2007) have nicely demonstrated that this may be related to the increase of low concentrations of environmental like-estrogen compounds. These estrogen-like compounds, called xenoestrogens, are present in the environmental pollutants mainly in water and food. They are able not only to activate MCs but enhance MC degranulation upon allergen cross-linking of IgE which may explain the above described increment of allergic diseases in the last years in developing countries (Narita et al., 2007).

In an animal model of allergic disease, the role of female sex hormone was tested. Female mice have reportedly an increased susceptibility to allergic airway disease in compared with male mice (reviewed in Carey et al., 2007). Levels of IgE are much higher in allergic female mice compared to their syngeneic male (Corteling and Trifilieff, 2004). Female rats that underwent ovariectomization developed less airway inflammation compared with sham controls animals (Ligeiro de Oliveira et al., 2004). However, estrogen replacement in the ovariectomized animals re-established airway inflammation levels of intact females (Ligeiro de Oliveira et al., 2004). Treatment of intact female rats with the selective estrogen receptor antagonist tamoxifen also reduced the development of allergic airway disease (Ligeiro de Oliveira et al., 2004). Thus, the direct effect of these hormones on disease development is hereby demonstrated.

Beyond the well-documented effects of estradiol and progesterone on MC function in MC-associated diseases, these hormones were further implicated in controlling different MC process under physiological conditions. For instance, estradiol was showed to be a potent inducer of ovarian MC degranulation, which seems to be a necessary factor during the process of oocyte ovulation (Jaiswal and Krishna, 1996; Tamura and Kogo, 1999).

MC NUMBER, MATURATION, AND DEGRANULATION IN THE UTERUS ARE UNDER THE CONTROL OF FEMALE SEX HORMONES

The presence of MCs in the uterus has been already described in many species including human (Drudy et al., 1991), mouse (Padilla et al., 1990), rat (Aydin et al., 1998), hamster (Harvey, 1964) as well as goat (Karaca et al., 2008). Besides, the number of MCs in the uterus was shown to fluctuate during estrous cycle suggesting an influence of female sex hormones on MC recruitment to the uterus (Aydin et al., 1998). Ovariectomized mice, in which estradiol and progesterone are almost absent, have less number of uterine MCs compared to control, non-ovariectomized animals (Jensen et al., 2010). Hormonal replacement, estradiol alone or in combination with progesterone, restored the number of uterine MCs after ovariectomization, which was comparable to the levels observed in control mice (Jensen et al., 2010). Hormonal replacement additionally induced an augmentation in the levels of MC-related proteases expression in the uterus as well as boosted MC degranulation (Jensen et al., 2010). This is of particular importance because upon degranulation, MCs release several molecules (histamine, proteases, metalloproteinases, pro-angiogenic factors), all very well known to account for the process of embryo implantation.

CONCLUSION

Mast cells, the so-called unicellular glands, once solely known as effectors cells of the innate immune system only activated by IgE cross-linking to the IgE receptor upon allergen stimulation are now known to be much more plastic and susceptible to be activated by several factors including female sex hormones, estradiol and progesterone. Strong data in the last years reinforced the idea that these hormones are crucial component of MC behavior not

only in physiological conditions but also in several MC pathological situations. Deciphering the mechanisms by which female sex hormones activate MCs and under which conditions these happens, alongside with explanation why female sex hormones have these effects is of crucial interest for a better understanding of the physiology of these cells.

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