GENDER DIFFERENCES IN NEUTROPHIL FUNCTION AND CYTOKINE-INDUCED NEUTROPHIL CHEMOTACTANT GENERATION IN ENDOTOXIC RATS

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Abstract—Several lines of evidence indicate sexual dimorphism in the immune response. We explored gender differences in phagocytosis by neutrophils (PMNs), CD11b/c expression, generation of cytokine-induced neutrophil chemoattractant (CINC) and the influence of developmental stages on some of these parameters. Phagocytosis by PMNs of reproductive female rats was not suppressed by anesthesia and surgery as it was in age-matched males. The phagocytic response to an endotoxin (ET) challenge was also higher in PMNs of reproductive females than in males or in prereproductive or postreproductive females. CINC generation in reproductive females was lower than in age-matched males. Phagocytosis in saline-treated postreproductive females was reduced compared to reproductive and prereproductive females, but was not different from adult males. CD11b/c expression was greater in PMNs of salinetreated postreproductive females, than in reproductive or prereproductive animals, but an ET challenge upregulated CD11b/c expression to the same level in all three groups. No gender difference was observed in this parameter. These data indicate that in terms of phagocytosis PMNs of reproductive female rats are more resistant to the effects of anesthesia and surgery and respond to an ET challenge more vigorously than cells of age-matched males. CINC generation in adult rats is also gender dependent. The developmental stages in females modulate phagocytosis and β2-integrin expression in PMNs.

INTRODUCTION

Several lines of evidence indicate sexual dimorphism in the immune response and in the neuroendocrine-immunological aspects of the acute phase in the inflammatory process. Immunoglobulin levels are higher in females, along with more resistance to a variety of bacterial, viral and parasitic infections (1). In both experimental animals and in man, females demonstrate greater humoral
and cell-mediated responses to exogenous antigens than males of the same species, age and physiological conditions (1–3). Considerable evidence supports a role for sex steroids in autoimmune diseases both in the immunomodulation of the disease process and in their etiology (4–5). Altered immune responses have also been noted both in experimental models and in humans in pregnancy (6, 7) implicating possible sex hormonal regulation of macrophage function and lymphocyte activation.

The effects of sex hormones on chemotaxis of human peripheral polymorphonuclear leukocytes and monocytes have been investigated in the peripheral blood of healthy adults. Chemotaxis of PMNs was enhanced by progesterone, while it was reduced by estradiol. Random migration of PMNs was also affected in a similar fashion. The effect of estradiol on PMN chemotaxis was inhibited by addition of anti-estrogens or progesterone. Testosterone did not have a measurable effect on this parameter. Sex hormones have no effect on the chemotaxis of monocytes (8). These results suggest that sex hormones may modulate the altered PMN chemotaxis associated with gingival inflammation.

Specific estrogen receptors have been demonstrated in a number of cell types associated with important immunological functions, e.g. human peripheral blood monocytes (9), T suppressor/cytotoxic subsets (10) and macrophages (11). Several aspects of macrophage function are modulated by estrogens, e.g. increased phagocytic activity (12), increased expression of Ia in the production of interleukin-1 in vivo (13), and increased interleukin-1 production (14) are associated with estrogen stimulation.

Activated monocytes and macrophages secrete a wide array of inflammatory mediators. Gonadal steroids have been linked with production of IL-1, suggesting a new experimentally accessible interface between the neuroendocrine and immune systems (15). A reciprocal relationship between IL-1 mRNA levels in cultured human peripheral monocytes and progesterone and estradiol levels has been demonstrated (16). The release of PGE₂, one of the lipid mediators of the inflammatory process by murine peritoneal macrophages is decreased when progesterone level is increased during pregnancy (6).

The protective cardiovascular action of estrogen was studied in endotoxin shock (17–19). Estrogen also influences the responsiveness of vascular beds to catecholamine and other vasoactive substances (20), and the reticuloendothelial system (21).

We have previously characterized several effects of a short term endotoxin infusion or abdominal sepsis on various forms of the host defense mechanism involving the expression of adhesion molecules, phagocytosis, nitric oxide and superoxide generation and changes in arachidonic acid metabolism (22–30). Recently we demonstrated resistance to the negative immunomodulatory effects of anesthesia/surgery by blood PMNs of female rats, in terms of phagocytosis as compared to cells of age-matched males. The phagocytic response of PMNs