0163-769X/07/$20.00/0
*Printed in U.S.A.*

Endocrine Reviews 28(5):521–574

doi: 10.1210/er.2007-0001

# The Complex Role of Estrogens in Inflammation

Rainer H. Straub

*Laboratory of Experimental Rheumatology and Neuroendocrino-Immunology, Division of Rheumatology, Department of Internal Medicine I, University Hospital, 93042 Regensburg, Germany*

**There is still an unresolved paradox with respect to the immunomodulating role of estrogens. On one side, we recognize inhibition of bone resorption and suppression of inflammation in several animal models of chronic inflammatory diseases. On the other hand, we realize the immunosupportive role of estrogens in trauma/sepsis and the proinflammatory effects in some chronic autoimmune diseases in humans. This review examines possible causes for this paradox.**

**This review delineates how the effects of estrogens are dependent on criteria such as: 1) the immune stimulus (foreign antigens or autoantigens) and subsequent antigen-specific immune responses (*e.g.*, T cell inhibited by estrogens *vs.* activation of B cell); 2) the cell types involved during different phases of the disease; 3) the target organ with its specific microenvironment; 4) timing of 17β-estradiol administration in relation to the disease course (and the reproductive status of a woman); 5) the concentration of estrogens; 6) the variability in expression of estrogen receptor α and β depending on the microenvironment and the cell type; and 7) intracellular metabolism of estrogens leading to important biologically active metabolites with quite different anti- and proinflammatory function. Also mentioned are systemic supersystems such as the hypothalamic-pituitary-adrenal axis, the sensory nervous system, and the sympathetic nervous system and how they are influenced by estrogens.**

**This review reinforces the concept that estrogens have antiinflammatory but also proinflammatory roles depending on above-mentioned criteria. It also explains that a uniform concept as to the action of estrogens cannot be found for all inflammatory diseases due to the enormous variable responses of immune and repair systems. (*Endocrine Reviews* 28: 521–574, 2007)**

I. Introduction
II. Estrogen Receptors in Inflammation and Hypoxia
III. Estrogen Modulation of Specific Target Cells
  A. Estrogens and human peripheral blood mononuclear cells or whole cell cultures
  B. Estrogens, the B cell, and antibodies
  C. Estrogens and the T cell
  D. Estrogens and the monocyte/macrophage/dendritic cell
  E. Estrogens and macroglial/microglial cells
  F. Estrogens and natural killer cells
  G. Estrogens and fibroblast
  H. Estrogens and vascular smooth muscle cells
  I. Summary
IV. Estrogens and Inflammatory Factors
  A. Nuclear factor κB
  B. Adhesion molecules
  C. IL-1, IL-2, IL-6, IL-8, IL-12, TNF, IFN-γ—studies *in vitro*
  D. IL-4, IL-10, TGF-β—studies *in vitro*
  E. Estrogens and growth factors
  F. Estrogens and nitric oxide
  G. Estrogens and oxygen radicals
V. Estrogens and Apoptosis
VI. Estrogens and Migration of Leukocytes
VII. Estrogens and Angiogenesis
VIII. Estrogens Modulate Inflammatory Processes: Diseases and Models
  A. Arthritis
  B. Systemic lupus erythematosus
  C. Brain inflammation
  D. Thyroiditis
  E. Intestinal and liver inflammation
  F. Renal inflammation
  G. Inflammation of the lung and heart
  H. Eye inflammation
  I. Inflammation in the pancreas
  J. Prostatitis
  K. Endometriosis
  L. Injury: wound repair, trauma, and shock
  M. Bone resorption
  N. Summary
IX. Timing of Estrogen Administration in Relation to the Time Point of an Inflammatory Disease
X. The Role of Estrogen Metabolites in Inflammation
XI. Pregnancy and Inflammation
XII. The Contraceptive Pill, Hormone Replacement Therapy, and Inflammation

**First Published Online July 19, 2007**

Abbreviations: AP-1, Activator protein-1; CEE, conjugated equine estrogens; CI, confidence interval; E1, estrone; E2, 17β-estradiol; E3, estriol; EAE, experimental autoimmune encephalitis; ER, estrogen receptor; ERT, estrogen replacement therapy; FasL, Fas ligand; FoxP3, forkhead box P3; HPA, hypothalamic-pituitary-adrenal; HRT, hormone replacement therapy; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IκB, inhibitor of NF-κB; IL-1ra, IL-1 receptor antagonist; iNOS, inducible NOS; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein; MMP, matrix metalloproteinase; MS, multiple sclerosis; NF-κB, nuclear factor κB; NO, nitric oxide; NOS, NO synthase; OC, oral contraceptives; OR, odds ratio; PBMCs, peripheral blood mononuclear cells; RA, rheumatoid arthritis; RANK, receptor activator of NF-κB; RANKL, RANK ligand; RANTES, regulated on activation normally T cell expressed and secreted; ROS, reactive oxygen species; RR, relative risk; SLE, systemic lupus erythematosus; SNS, sympathetic nervous system; Th1, T helper type 1; Th2, T helper type 2; Th17, T helper type 17; TIMP, tissue inhibitor of MMPs; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

*Endocrine Reviews* **is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

A. The contraceptive pill
B. Hormone replacement therapy
XIII. Estrogens and Systemic Response Systems
A. The hypothalamic-pituitary-adrenal axis
B. The sensory nervous system
C. The sympathetic nervous system
D. Summary
XIV. The Dual Role of Estrogens and Consequences for Autoimmune Disease
XV. Discussion
A. Autoimmune diseases: the initiation phase
B. Autoimmune diseases: the symptomatic phase
C. Inflammatory diseases with involvement of infectious agents
D. Inflammatory diseases with mild inflammation without infectious agents
E. Inflammatory fibrogenesis in liver and kidney
XVI. Conclusions

## I. Introduction

IT IS WIDELY ACCEPTED that females of all ages experience significantly lower rates of infection and resultant mortality than men. This significant difference in the inflammatory response of women compared with that of men has long been noted (1, 2). This heightened inflammatory response is advantageous in response to infection and sepsis but is unfavorable in immune responses against self, leading to an overall increased rate of autoimmune diseases in women compared to men (2, 3). Epidemiological and immunological evidence has suggested that female sex hormones play a role in the etiology and course of chronic inflammatory diseases because the menstrual cycle, pregnancy, and menopausal status are important influencing factors (2, 4, 5).

In a previous review, the role of the menopause on proinflammatory cytokine activity has been extensively studied (6). This review focused on the increase of proinflammatory cytokines with the menopause (the fall of estrogens and other gonadal steroids), but this review only marginally touched chronic inflammatory diseases. Another review on gonadal steroids and T and B cell immunity was presented 10 yr ago, but since then, a lot of new information has been generated (2). This is particularly true with respect to chronic diseases that formerly have not been allocated to "inflammatory diseases" such as bone resorption. This is important because incidence rates over age for osteoporosis match incidence rates over age for, *e.g.*, rheumatoid arthritis (RA). Furthermore, the progress in animal models of chronic inflammation was immense, and a good portion of this information has been published after 1996.

There is still the unresolved paradox with respect to the immunomodulating role of estrogens. On one side, we recognize inhibition of bone resorption and suppression of inflammation in several animal models of chronic inflammatory diseases. On the other side, we realize the immune supportive role in trauma/sepsis and the proinflammatory effects in some chronic autoimmune diseases in humans (as an initiating or perpetuating factor). This review examines possible causes for this paradox and suggests a solution in the *Discussion* (*Section XV*).

Because the author has been confronted by an enormous quantity of literature (approximately 5200 references in the primary retrieval), this review only focuses on estrogens. It is evident that androgens and progesterone are important in inflammation, but presentation of these subjects was not possible due to space constraints. Throughout the text, tables, and figures, the Système International unit for the concentration is given as moles/liter (abbreviated with M).

## II. Estrogen Receptors in Inflammation and Hypoxia

The presence of estrogen receptors (ERs), ERα and ERβ, is of outstanding importance because a preponderance of one ER subtype over the other might change estrogen effects (7, 8). For instance, in synovial tissue of patients with RA, macrophage-like and fibroblast-like synoviocytes were positive for ERα (9–11) and ERβ (12). Importantly, one study demonstrated higher density of ERβ+ cells than of ERα+ cells (13). Others demonstrated a higher density of ERβ+ cells in relation to ERα+ cells in RA synovial tissue compared with controls (12). ERβ preponderance was observed in all three synovial compartments investigated: in the lining cell layer, in fibroblasts, and in inflammatory cells (12). Similarly, the amount of ERα was lower in T cells of patients with systemic lupus erythematosus (SLE) than controls, but the quantity of ERβ was similar, which indicates a relative increase of ERβ in relation to ERα in SLE patients (14). In animals subjected to trauma and hemorrhage, a general inflammatory condition, ERβ mRNA expression was increased, whereas ERα expression was decreased (15). These studies suggest inflammation-dependent up-regulation of ERβ relative to ERα.

It was further demonstrated that hypoxia, which typically accompanies inflammatory conditions, reduced expression of ERα (16, 17), and oxidative stress increased the expression of ERβ (18). In endothelial cells (E304), oxidative stress increased ERβ relative to ERα. In activated macrophages, lipopolysaccharide (LPS) plus interferon (IFN)-γ in the presence of hypoxia increased expression of ERβ but not of ERα (18). These studies support a concept of up-regulation of ERβ relative to ERα under hypoxic conditions, which might lead to a preponderance of signaling through ERβ pathways.

The preponderance of ERβ relative to ERα under inflammatory and hypoxic conditions might influence estrogen effects. One might hypothesize that this depends on the time point of estrogen application in relation to the state of an inflammatory disease. A situation before disease outbreak or at the beginning of a disease with slight tissue inflammation and little hypoxia might be governed by a balance of ERα and ERβ, whereas in the chronic phase of a disease with much inflammation and a higher degree of hypoxia, ERβ is increased relative to ERα. In such a situation, ERβ-mediated cross-modulation of ERα, *e.g.*, demonstrated as ERβ-mediated inhibition of ERα-stimulated IL-1 secretion (8), might play an important role in the chronic disease course.

## III. Estrogen Modulation of Specific Target Cells

This section delineates effects of estrogens on cells relevant to inflammation. In most situations, this reflects investigation