

Sex hormones in Sjögren's syndrome

Hans Carlsten

Department of Rheumatology, Sahlgrenska University Hospital, Göteborg, Sweden

Autoimmune diseases have a strong female preponderance. For instance, in SLE and RA, 90 and 70% of the patients are women, respectively. Also, the great majority of patients with Sjögren's syndrome are females. It is still unclear by what mechanism females become more susceptible to autoimmune diseases. In the case of Sjögren's syndrome some experimental data points out sex steroid hormones as being partly responsible for this female dominance.

Estrogens are known since long to exert immunoregulatory properties in mice. We have proposed a dual effect of estradiol on immune reactivity as demonstrated, by on one hand, suppressive effect on T lymphocyte mediated inflammation and stimulation of immunoglobulin production on the other. This estrogen mediated dichotomous impact on immunity results in suppression of T lymphocyte dependent diseases such as experimental collagen type II induced arthritis and encephalomyelitis whereas immune-complex mediated diseases such as murine systemic lupus erythematosus (SLE) is aggravated. Lupus prone NZB/W and MRLlpr/lpr mice spontaneously develop salivary and lacrimal gland inflammation with focal infiltration of T lymphocytes around blood vessels and glandular ducts resembling the findings in salivary gland biopsies in patients with Sjögren's syndrome. In long term studies treating castrated lupus mice with physiological doses of 17 β -estradiol we demonstrated significant suppression of submandibular T lymphocyte infiltration (1–3). However, it should be noted that in a short-term treatment study the authors did not demonstrate any significant effect of 17 β -estradiol on murine salivary gland inflammation (4). Until now, no clinical study on the effect of estrogen on Sjögren's syndrome has been published.

Testosterone treatment of murine models of Sjögren's syndrome causes significant suppression of inflammation in submandibular and lacrimal glands, reviewed in (5). These results may well be explained by the known immunosuppressive properties of testosterone (6). Some case reports indicate that androgens could have beneficial effects in patients with Sjögren's syndrome but no controlled study is yet available.

Taken together, experimental data indicate that male sex steroid hormones are potentially protective whereas estrogens are mildly protective against the development of chronic T lymphocyte inflammation in Sjögren's syndrome. Until reliable controlled clinical studies are available we can only speculate if hormone treatment can be recommended in patients. Nevertheless, since the vast majority of Sjögren's syndrome sufferers are women it is important to consider if estrogen containing contraceptives or hormone replacement therapy should be recommended or not. No clear-cut answer can be given to this question. However, the above discussed findings in animal models of Sjögren's syndrome as well as the known suppressive effect of estrogen on T lymphocyte mediated immunity in humans make it tempting to recommend, in applicable cases, both types of hormone therapy in female Sjögren's syndrome patients. In contrast, in rare cases of patients with severe disease characterised by symptoms of immune complex manifestations sometimes demonstrated by complement consumption, my personal opinion is to avoid estrogens in any form. There are too many indications that estrogens can stimulate autoantibody formation and thereby aggravating immune complex disease.

The mechanisms whereby sex steroids modulate the course of chronic T lymphocyte inflammation are not known. During the last years several reports indicate that exposure to sex steroids can modulate local production of cytokines in salivary and lacrimal glands, reviewed in (5). Still we don't know the exact molecular background to these effects. In the case of estrogen the discovery of a second estrogen receptor (7) (named ER- β whereas the earlier known ER is renamed

ER-) can give new clues to the understanding of the complex effects of this hormone on immune responses, especially in autoimmune rheumatic diseases.

References

1. Carlsten H, Tarkowski A. Histocompatibility complex gene products and exposure to estrogen: two independent disease acceleration factors in murine lupus. *Scand J Immunol* 1993; 38: 341-347.
2. Carlsten H, Nilsson N, Jonsson R et al. Estrogen accelerates immune complex glomerulonephritis but ameliorates T cell mediated vasculitis and sialadenitis in autoimmune MRL lpr/lpr mice. *Cell Immunol* 1992; 144: 190-202.
3. Carlsten H, Nilsson N, Jonsson R, Tarkowski A. Differential effects of oestrogen in murine lupus: acceleration of glomerulonephritis and amelioration of T cell mediated lesions. *J Autoimmunity* 1991; 4: 845-856.
4. Sato EH, Sullivan DA. Comparative influence of steroid hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjogren's syndrome. *Invest Ophthalmol Vis Sci* 1994; 35: 2632-42.
5. Sullivan DA. Sex hormones and Sjögren's syndrome. *J Rheumatol* 1997; 24: 17-32.
6. Carlsten H, Holmdahl R, Tarkowski A, Nilsson L-Å. Oestradiol and testosterone mediated effects on the immune system in normal and autoimmune mice are genetically linked and inherited as dominant traits. *Immunology* 1989; 68: 209-214.
7. Enmark E, Pelto-Huikko M, Grandien K et al. Human estrogen receptor beta-gene structure, chromosomal localization, and expression pattern. *J Clin Endocrinol Metab* 1997; 82: 4258-65.