Prolactin, an immunostimulating peptide hormone, is linked with a number of rheumatic diseases. In this issue of The Journal, Vera-Lastra and associates report a trend toward elevated basal prolactin concentrations in scleroderma. The authors also found significant hyperresponsiveness to metoclopramide stimulation associated with pituitary microadenomas in the majority of subjects with diffuse and limited cutaneous scleroderma.

Prolactin is a growth factor for lymphocytes with the potential to stimulate immune responses at many levels. Prolactin is a cytokine. It has comparable structural motifs, is synthesized in multiple sites including the anterior pituitary and lymphocytes, and has similar receptor structures and signal transduction pathways. Prolactin receptors are distributed throughout the immune system and are members of a novel receptor family that includes receptors for interleukin 2β (IL-2β), IL-3, IL-4, and IL-6. The transcription factor gene, interferon regulatory factor-1 (IRF-1), is exquisitely sensitive to prolactin and is an important regulator of T cell and B cell differentiation and maturation. IRF-1 is required for Th1 responses. Prolactin, which stimulates IRF-1, can regulate Th1 cytokines such as interferon-γ and IL-15.

Hyperprolactinemia stimulates autoimmune disease, and this stimulation is determined by genetics. The estrogen-sensitive transgenic R2A gamma 2b BALB/c mouse was oophorectomized to remove the major source of estrogen and treated with prolactin to achieve a 2-fold increase in circulating prolactin. These hyperprolactinemic animals, but not mice transgenic for R4A gamma 2b, developed lupus-like serology with inversion of the T1/T2 ratio, increased B cells, and increased Bcl-2. Further, prolactin-deficient mice developed DNA-reactive B cells that were functionally inactive. It therefore appeared that adequate circulating prolactin was required for estrogen to stimulate the lupus phenotype in a lupus-prone mouse with a permissive genetic background.

Autoantibodies have been detected in hyperprolactinemic individuals without clinical autoimmune disease. Women with prolactinomas had anti-microsomal and anti-thyroglobulin antibodies, each occurring in 21% of subjects, and anti-thyroglobulin antibodies were present in 19% of hyperprolactinemic men. In a survey of hyperprolactinemic women (82% with pituitary adenomas), one or more autoantibodies were found in 76%, and 24% had at least 7 autoantibodies. The most common antibody specificities were single- and double-stranded DNA, Sm, pyruvate dehydrogenase, and SSA. Elevated prolactin concentrations were found in 12% of serum samples submitted to a university laboratory for autoantibody testing. High prolactin was associated with the diagnosis of systemic lupus erythematosus (SLE) and antibodies to SSA and SSb.

Many surveys have shown that basal prolactin concentrations are increased in patients with rheumatic diseases. Levels that exceed the norm were identified in reactive arthritis, scleroderma, Sjögren’s syndrome, rheumatoid arthritis, chronic juvenile arthritis, and SLE. In contrast, hyperprolactinemia was not found in patients with ankylosing spondylitis or Behçet’s syndrome. Fifteen of 21 hyperprolactinemic women met criteria for the diagnosis of fibromyalgia, but 15 women with primary fibromyalgia had normal serum prolactin and normal responses to hypoglycemic stimulation.

Why is serum prolactin elevated in some patients with rheumatic diseases? About one-third of all hyperprolactinemic individuals have idiopathic hyperprolactinemia, and remain so for years without evidence of pituitary adenomas. Hypothyroidism and renal insufficiency are not uncommon in autoimmune disorders, and both conditions are associated with hyperprolactinemia. Medications, especially neuroleptic agents including phenothiazines, reserpine, and methyl dopa are also responsible for elevated prolactin.

The report of Vera-Lastra describes 30 patients with scleroderma, all treated with D-penicillamine, whose baseline prolactin levels showed a trend to exceed healthy controls. D-penicillamine has a well known association with mammary gigantism, and some women with rapid breast enlargement were hyperprolactinemic. The question arises, therefore, whether the patients in the current study had drug-induced hyperprolactinemia. There is little information concerning prolactin levels in D-penicillamine treat-

See Functional hyperprolactinemia and hypophyseal microadenoma in SSc, page 1108
circulating 60 kDa prolactin that could affect pituitary feed-
or prolactin and serve as an extra pituitary source of bioactive
gals with lupus10, and it has been proposed that the non-cycling
abnormal to metoclopramide.

Prolactinomas have been reported in at least 43 individu-
with lupus10, and it has been proposed that the non-cycling
secretion of abnormally high concentrations of prolactin stim-
ates autoimmune responses and contributes to the patho-
genesis of SLE. These prolactinoma-bearing patients with
lusus, however, have not been studied for hypothalamic func-
tion with standard tests designed to evaluate responses to thy-
roid stimulating hormone or metoclopramide.

The link between microadenomas, hypothalamic func-
tion, and autoimmunity offers a rich field in which to
explore the effects of dopamine and the hypothalamus on
the immune system. It appears that SLE, scleroderma, and
possibly other autoimmune diseases may share defects in
dopamine regulation that reflect basic abnormalities in
neuroendocrine regulation.

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