Editorial

Impaired Hypothalamic Function, Prolactinomas, and Autoimmune Diseases

Prolactin, an immunostimulating peptide hormone, is linked with a number of rheumatic diseases. In this issue of *The Journal* Vera-Lastra and associates[1] 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 2ß (IL-2ß), IL-3, IL-4, and IL-6[2]. 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[3,4].

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[5,6].

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[7]. 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[8]. 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[9].

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[2].

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 methyldopa are also responsible for elevated prolactin[10].

The report of Vera-Lastra[1] 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[1] had drug-induced hyperprolactinemia. There is little information concerning prolactin levels in D-penicillamine treat-

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ment, and this question cannot be answered definitively. The authors[1] contend that prolactin was not affected by medication in their subjects, none of whom had the breast enlargement syndrome. Drug-induced breast hyperplasia has been described mostly in isolated case reports, and prolactin was measured in the reported individuals only after breast enlargement occurred. Scleroderma patients developing mammary hyperplasia have been either hyperprolactinemic or normoprolactinemic, and histological examination of breast tissue showed mainly connective tissue and no changes in the glandular tissue[11,12].

The secretion of pituitary prolactin is under the inhibitory control of the hypothalamus, and the most important inhibiting factor is dopamine. Dopamine agonists such as bromocriptine cause a sharp drop in prolactin levels in normal individuals and in the presence of prolactin-secreting adenomas[10]. Anti-prolactin antibodies have been identified in SLE patients with idiopathic hyperprolactinemia. It is possible that anti-prolactin activity interferes with attachment of prolactin to receptors, causing the pituitary to "see" a false low level of prolactin so that feedback mechanisms involved in the regulation of prolactin secretion are disrupted[13]. It is also possible that activated lymphocytes secrete prolactin and serve as an extra pituitary source of bioactive circulating 60 kDa prolactin that could affect pituitary feedback and be detected in a prolactin assay[14,15]. These putative mechanisms of hyperprolactinemia, however, have not been investigated in scleroderma.

Vera-Lastra and associates[1] show that 2 mechanisms involving abnormal secretion of prolactin that were identified in SLE — hypothalamic dysfunction and prolactinomas — can also be operative in scleroderma. Of interest, dysregulation of prolactin secretion was linked to pituitary adenomas in scleroderma patients.

Impaired hypothalamic function has been invoked as a contributor to hyperprolactinemia in SLE, and evidence exists that impaired dopamine turnover and altered dopaminergic tone are associated with high prolactin in lupus[16]. Twenty-five of the 30 patients with scleroderma studied by Vera-Lastra[1] responded to metoclopramide challenge with excessive prolactin secretion that clearly exceeded the values in controls. Twenty-four of these responders had microadenomas that are assumed to be prolactinomas. In contrast, only one of the 6 subjects without microadenomas responded abnormally to metoclopramide.

Prolactinomas have been reported in at least 43 individuals with lupus[10], and it has been proposed that the non-cycling secretion of abnormally high concentrations of prolactin stimulates autoimmune responses and contributes to the pathogenesis of SLE. These prolactinoma-bearing patients with lupus, however, have not been studied for hypothalamic function with standard tests designed to evaluate responses to thyroid stimulating hormone or metoclopramide.

The link between microadenomas, hypothalamic function, 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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