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SEX HORMONES IN THE PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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1. ABSTRACT

Sex hormones – estrogens, progestins, androgens, and prolactin – have well-documented effects on the development, progression, or severity of systemic lupus erythematosus (SLE). These effects are complex and are confounded by *in vitro* and *in vivo* considerations that obscure a simple explanation of the sexual dichotomies in SLE. An overview of available experimental and clinical data suggests that low androgens and abnormalities in the prolactin-gonadal axis are the most consistent hormonal aberrations found in human SLE. Additional studies focusing on interactions of gonadal steroids with prolactin and other pituitary hormones should expand our understanding of the role of sex hormones in the pathogenesis of SLE and strengthen the potential of hormonal immunotherapy.

2. INTRODUCTION

The purpose of this summary is to provide a panoramic overview of roles for sex hormones in the pathogenesis of systemic lupus erythematosus (SLE). Recent authoritative reviews of sex hormone effects in SLE are available (1-4) and clearly document the plethora of direct and indirect hormonal effects on experimental and clinical manifestations of lupus. However, a cohesive immunoendocrine schema appears lacking, due in part, to the relative absence of delineation of hormone-hormone interactions within the pituitary-gonadal axis. This review is designed to challenge traditional dogma that actions and effects of estrogen are primarily responsible for the female predilection of SLE. This concept must be challenged and expanded on the basis of several factors. The factors include, but are not limited to, investigations demonstrating

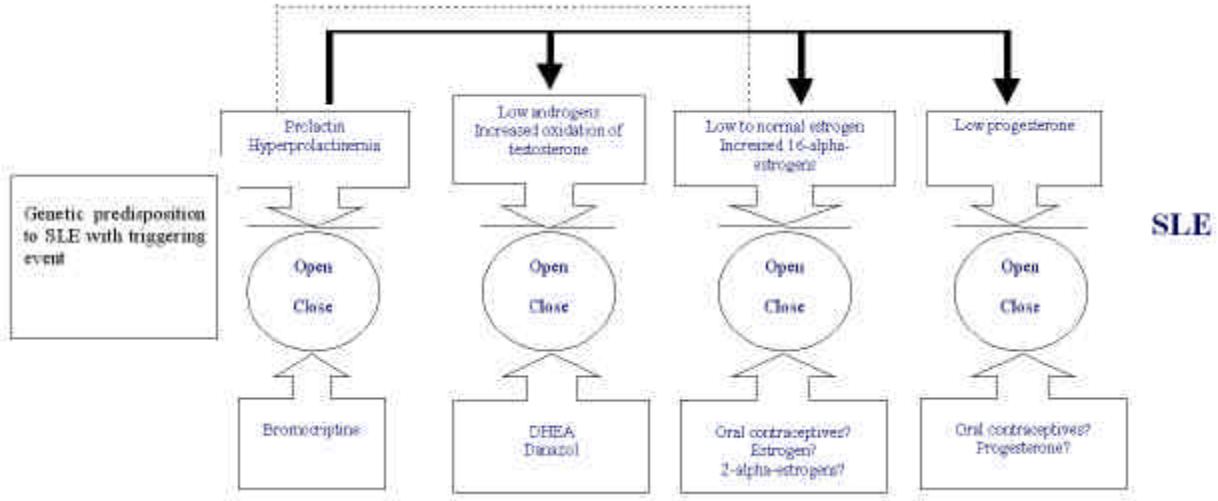

Figure 1. Immune and autoimmune abnormalities of lupus are caused by an inciting event in a predisposed individual (left block). The appropriate hormonal milieu (pipeline) facilitates progression or development of clinical lupus (right block). That milieu consists primarily of normal to high prolactin, low androgens and estrogens/progestogens, or altered androgen to estrogen ratios. Prolactin directly impacts on gonadal steroid production (solid line); estrogens (dashed line) stimulate pituitary prolactin secretion. Hormonal modulation by pharmacotherapy may prevent, suppress, or reverse the progression (pipeline) of clinical SLE.

that serum estrogen concentrations are typically low to normal in SLE patients and that prolactin, a significant immunostimulatory pituitary hormone, contributes to the development or manifestations of lupus while interacting with gonadal steroids. Moreover, data continues to establish that androgens, especially dehydroepiandrosterone (DHEA), an immunosuppressive sex hormone precursor, is important to lupus pathogenesis and its relative absence may permit SLE development or manifestations. Conversely, administration of DHEA raises not only androgen but also estrogen concentrations (see below). These novel concepts are extremely complex due to profuse hormone-specific and cell-specific actions and interactions.

Several general and specific *caveats* (Table 1) regarding interpretation of hormonal investigations of autoimmunity must be considered during the process of challenging traditional concepts. It must be pointed out that the majority of clinical investigations examining hormonal abnormalities in SLE contain fewer than 50 patients and, therefore, may not have incontrovertible statistical power. The vast majority of clinical studies did not examine well-established endocrinological interactions between estrogen, progesterone, DHEA, testosterone, and prolactin only represent "snapshots" in time that do not delineate the dynamics of daily, weekly, or monthly hormonal changes. For example, precursors to estrogen and testosterone include DHEA and progesterone (5). DHEA acts directly on the estrogen response element (ERE) (6) and may be ultimately converted to estrogen or testosterone (5,7). Testosterone is also aromatizable to estrogen (5,8,9). Estrogen stimulates prolactin secretion (10,11) and prolactin suppresses gonadal steroid secretion (5,10) and modulates peripheral androgen metabolism (12). Conversely, suppression of prolactin by bromocriptine increases estrogen and androgen concentrations (13-16).

These complex feedback loops are further confounded by SLE-specific hormonal anomalies: increased hydroxylation of estradiol, increased oxidation of testosterone (17,18), inadequate production of progesterone (19), and associations with prolactin abnormalities (20-22). Additional challenges to traditional concepts of SLE hormonal modulation include reports that oral contraceptives elevate prolactin concentrations (23,24) and that estrogen concentrations are low or normal and prolactin levels are elevated in patients with active SLE (25). Accordingly, suppression of prolactin by bromocriptine suppresses SLE disease activity (26,27), an endocrine therapy that typically increases estradiol in women (15,28). In two separate murine lupus models, estrogen, stripped of its prolactin stimulating properties by bromocriptine administration, suppressed the development of immune complex glomerulonephritis (29,30). These latter findings provide a basis for formulating novel concepts of sex hormonal modulation of lupus pathogenesis.

It is unlikely that sex hormones "cause" lupus *per se*, but rather, that sex hormones act as "flow" valves along a pipeline of autoimmune models or individuals with a predisposition to the development of SLE (see figure 1). Although one might conceive of situations in which hormones or hormonal xenobiotics precipitate autoimmunity through effects on apoptosis or antigen presentation, it seems more plausible at this time, that sex hormones provide a milieu that facilitates development or progression of autoimmune disease manifestations. Specific immunomodulatory valves controlled by sex hormones may occur through a variety of mechanisms described in Table 2 and reviewed below.

For the purpose of this review, sex hormones will be defined as those that differ significantly between

Table 1. *Caveats* of interpreting roles of sex hormones in SLE pathogenesis

- Most studies involve small numbers of patients
- Most studies do not explore the complexities of the pituitary gonadal axis
- Each sex hormone has cell specific effects
- Each sex hormone has cytokine specific effects
- Each sex hormone has hormone specific effects
- Short and long term effects may differ
- Physiologic vs. pharmacologic effects differ
- Steroid interconversions occur in vitro and in vivo and many of the gonadal steroid hormones are precursors to estrogen
- Androgens (DHEA/testosterone) may be converted to estrogen in vivo and may act on the estrogen response element
- Estrogen receptor blockers have estrogen agonist and antagonist activities
- Estrogen and prolactin are inextricably linked in vivo
- Prolactin suppresses estrogen and androgen production
- Bromocriptine suppresses prolactin secretion and may elevate estrogen or androgen concentrations secondarily

Table 2. Immunomodulatory effects of sex hormones

Estrogen

- Suppresses T lymphoproliferation and function
- Suppresses IL-2 and TNF-alpha
- Stimulates IFN-alpha, IL-5, IL-10
- Correlated with IL-4 production
- Stimulates B cell survival
- Stimulates antibody and autoantibody production

Progesterone

- Stimulates IL-4 production

DHEA/Testosterone

- Stimulates IL-2 production
- DHEA-sulfate correlated with IFN-gamma in vivo

Prolactin

- Associated with lymphoproliferation
- Co-mitogenic with IL-2
- Stimulates IFN-gamma
- Stimulates antibody and autoantibody production
- Stimulates IL-2 receptor expression
- Immunoreactive or lymphocyte prolactin production has autocrine effects
- Prolactin receptor belongs to the cytokine receptor superfamily

females and males: estrogen, progesterone, testosterone, DHEA, and prolactin. An additional tier of complexity occurs in females, who endure dramatic hormonal increases of every sex hormone during pregnancy, followed by a precipitous fall in the post-partum period, with the exception of prolactin (5,10). While corticosteroids, growth hormone, follicle stimulating and luteinizing hormone, and pregnancy-specific hormones - human placental lactogen (HPL) and human chorionic gonadotropin (HCG) - also differ between the sexes and likely have significant immunomodulatory effects, their contributions to hormonal immunomodulation in SLE is relatively unknown and beyond the scope of this review.

Immunoendocrine evidence that sex hormones contribute to the pathogenesis of SLE occurs primarily at five distinct levels that are not necessarily interdependent: experimental animal models, clinical associations or observations, epidemiologically-structured studies, pharmacological manipulations, and molecular mechanisms of action. A simple and straightforward endocrinological approach to defining roles of sex hormones in the pathogenesis of lupus is to stratify investigations as above and examine the congruence of hormone administration and hormone removal or blockade within each stratum of evidence. Lack of extension, at all levels of hormonal immunomodulatory evidence, impedes a thorough understanding of the impact of sex hormones and the potential of hormonal immunotherapy in SLE. Herein key experimental animal model, clinical, epidemiological, pharmacological and molecular data regarding the roles of estrogen, testosterone/DHEA, progesterone, and prolactin in the pathogenesis of SLE are summarized and conclusions are posited.

3. ESTROGEN

Initial endocrinological studies of sex hormone administration and withdrawal in SLE were conducted in murine models, especially the F_1 hybrid of New Zealand Black x New Zealand White (B/W) mouse model of SLE. The predilection for the development of SLE for the female species includes the B/W mouse (31-33). These observations have provided a strong impetus to identify the penultimate female sex steroid – estradiol and its variants – as the obvious and easiest explanation for sex differences in SLE disease pathogenesis and several studies have focused on cataloguing immune and autoimmune effects of this sex hormone. Estrogens are aromatized C-18 steroids synthesized in the gonads and adipose tissue by aromatization of testosterone or aromatization of androstenedione to estrone followed by its reduction to estradiol. The most potent circulating estrogen is 17-beta-estradiol (5).

3.1. Animal Studies

Original descriptions of the B/W mouse model of SLE established a sexual dichotomy for murine lupus and initiated extensive hormonal manipulations in attempts to delineate their regulatory roles in lupus (31-33). Female B/W mice develop autoimmune abnormalities sooner, higher levels of autoantibodies, and accelerated mortality compared to their male counterparts. Administration of 17-beta-estradiol or ethinyl estradiol accelerated mortality in gonadectomized female and male B/W mice (31-33). However, it must be recognized that, in these initial studies, complete necropsies were not performed and that the studies utilized pharmacological doses of estrogen, which accelerated renal insufficiency/mortality through the induction of bladder outlet obstruction and may have

increased autoantibody production through hyperprolactinemia (34). Two recent studies (29,30) demonstrate that estrogen immunostimulatory effects are abrogated when prevented from stimulating pituitary prolactin secretion by bromocriptine administration. In fact, at physiological concentrations, estrogenic actions alone to suppress murine lupus disease manifestations (29) and murine lupus T cell functions (35,36), an immunosuppressive effect of estrogen noted by others (37,38). It has been further noted, however, that gonadotropin agonists and antagonists also modulate murine lupus in castrated mice, without an effect on serum prolactin concentration, although effects on serum estrogen and progesterone concentrations despite gonadectomy (29), were not assessed (39).

Marked anomalies of estrogen metabolism or estrogen receptors contributing to the pathogenesis of murine lupus have not been identified in B/W mice (40,41). Moreover, removal of the ovaries, the primary source of estrogen in the female mouse (32), had no significant effect on murine lupus disease development or mortality, which, if gonadal estrogen or progesterone were primary immunostimulatory hormones, would be contradictory. Nevertheless, estrogen receptor blockade with nafoxidine or tamoxifen has been shown to suppress murine lupus (33,42,43); however, these drugs have both estrogenic agonistic and antagonist effects (44, 45), that may be cell specific. Therefore, until a more extensive immunoendocrine assessment of estrogen and its blockade is performed, the conclusion that estrogen agonism stimulates or estrogen antagonism ameliorates murine lupus is precluded.

3.2. Clinical associations/observations

The overwhelming female predominance for SLE begins at puberty and extends to menopause (46), supporting the concept that estrogens or other reproductive factors stimulate lupus development. This concept is further evidenced by reports of menstrual cycle flares of SLE (47), disease exacerbations by oral contraceptives (reviewed in 48,49) or estrogen administration (50,51), and induction of lupus by ovulation regimens (52,53). However, it should be recalled that oral contraceptives (23,24) and estrogen administration (10,11) might also increase secretion of immunostimulatory pituitary prolactin. Conversely, ovarian failure and, presumably, reduced estrogen concentrations, have been associated with reduced rates of lupus flares (54), although, as reviewed by others (55), estrogen replacement associated with post-menopausal ovarian failure is not clearly associated with abatement or recurrent lupus respectively.

3.3. Epidemiological examinations

There have been, to this author's review, only two studies that have demonstrated an association between increased estrogen concentrations and lupus (56,57). Additional descriptive epidemiological studies have examined sex hormones in female SLE patients (21,25,56-61), and suggested that sex hormone status may predict survival (62). Surprisingly, the majority of these studies have shown estrogen concentrations to be low or normal in SLE patients (21,24,58,60,61). Extension of studies to male lupus patients (63-69) have primarily concluded that androgens are low and estradiol, when measured (64-67), is normal, although one study found 4 of 13 male SLE patients were hyperestrogenemic (68).

A series of investigations has documented abnormal estrogen metabolism in SLE patients: increased 16-beta- hydroxylation of 17-beta-estradiol to estriol and reduced 2-alpha-hyroxylation to 2-methoxyestradiol (17). Estriol is known to be a strong stimulus for prolactin stimulation (10,11), whereas methoxyestradiol appears to suppress prolactin production (70). Abnormal aromatase activity and correlation of aromatase activity with estrogen levels has also been reported to occur in SLE patients (56).

A study that longitudinally examined pituitary-gonadal axis abnormalities in lupus patients during pregnancy (25) showed 17-beta-estradiol was suppressed and serum prolactin was elevated compared to healthy and rheumatoid arthritis pregnant control patients. Lupus disease activity correlated best with serum prolactin concentrations (25). The findings of abnormally low estrogen (71) and elevated prolactin (72) during lupus pregnancies have been independently confirmed. Similar to the lack of marked differences in estrogen concentrations between lupus patients and controls, estrogen receptors in lupus patients may not differ significantly from controls (73-75), although firm conclusions (76,77) await additional investigation.

3.4. Pharmacological manipulation

No double-blinded, placebo-controlled studies of estrogen administration to lupus patients have been published to this author's literature search, mostly retrospective trials or case controlled trials exist. As reviewed (55), there is no clear consensus on the effects of menopause and postmenopausal estrogen replacement on lupus disease pathogenesis. Potential clarification of this dilemma may be achieved by the NIH sponsored Safety of Estrogen in Lupus National Assessment (SELENA) trial. In small-scale clinical studies, administration of gonadotropic agents, cyproterone (78) or buserelin (79), reduced disease activity, possibly by altering estrogen:androgen ratios. Unexpectedly, estrogen receptor blockade by tamoxifen in humans, in contrast to murine models, did not improve and appeared to worsen disease activity (80), either due to estrogenic agonist effects of tamoxifen or blockade of immunosuppressive effects of estrogen. This result may also be explained by endocrinological actions of tamoxifen on the pituitary gonadal axis: abrogation of estrogenic (immunosuppressive) effects without changing prolactin levels (81). In contradistinction to estrogen blockade, administration of combination estrogen/progesterone oral contraceptives may improve cyclical lupus disease activity (82).

3.5. Molecular mechanisms

Despite confounded *in vivo* murine and human results, there remain several reasons to implicate estrogen in the pathogenesis of SLE, chief of which is estrogen's

effects on cytokines and B cell function (83). Estrogen appears to suppress lymphocyte production of IL-2 (84) and TNF-alpha (85). Additionally, 17-beta-estradiol appears to stimulate production of IFN-gamma (86-88), an abnormality noted to occur in female B/W mice (89). Estrogen has also been shown to stimulate IL-5 (90), and IL-10 (86,87), leading to a predominant Th2 cytokine profile consistent with excessive antibody or autoantibody production (91-93). Estrogens, while likely suppressive to T cell function, appear to support B cell survival (30), perhaps through prolactin stimulation. This is consistent with observations of cell-mediated immunosuppression and enhanced humoral immunity observed during the high estrogen:progesterone state of pregnancy (94).

Estrogen has also been shown to directly modulate bone marrow colony formation in murine lupus (95), lymphoblast transformation and IL-2 production of lymphocytes from lupus patients (96), and immunoglobulin and autoantibody production from mononuclear cells of SLE patients (97). Estrogen also appears to modulate lymphocyte signal transduction through effects on calcineurin, thus providing another conduit for estrogen modulation in lupus (98). Hence, several potential estrogen-induced molecular mechanisms - decreased IL-2 and TNF-alpha and increased IFN-gamma, IL-5 and IL-10 (99), increased immunoglobulin and autoantibody formation, and increased calcineurin – may act concomitantly to produce sex differences in lupus onset and prevalence. Based on an endocrinological paradigm of administration and withdrawal/blockade, available data document a role for estrogen, but this role may be immunosuppressive rather than stimulatory and is confounded by its prolactin-stimulating properties. Therefore, the role of estrogen in lupus pathogenesis is obscured by incongruent results of estrogen administration, withdrawal/blockade, or abrogation of its prolactin stimulatory effects. Furthermore, estrogen likely has effects in lupus which are cell-type dependent, that is, T-cell oppressive and B-cell supportive.

4. PROGESTERONE

Progesterone is a C-21 steroid produced predominantly by the gonads and adrenals, serving as an upstream precursor of both estrogen and testosterone. Progesterone concentrations rise significantly during the luteal phase of the menstrual cycle (5). The number of investigations of its role in lupus pathogenesis is markedly fewer than that for estrogen and testosterone. Nevertheless, available studies suggest that progesterone is lower in lupus patients than in controls (19,58,71).

4.1. Animal studies

Administration of progesterone, at pharmacological doses, accelerated lupus disease development and mortality in female and male B/W mice (31-33); however, these studies did not provide evidence of their endocrinological effects (*i.e.* effects on estrogen or prolactin) or necropsy examination for possible pharmacological or toxicological effects. In contrast, castration of female B/W mice did not improve disease activity or survival (32), suggesting either no major role for progesterone in murine lupus or compensated adrenal progesterone production. In a preliminary study, ovarectomy of female B/W mice leads to increased serum progesterone concentrations from a non-gonadal source, but did not markedly accelerate mortality (29). There have been no published studies on administration of anti-progestogens to B/W mice to provide additional data on the effects of progesterone.

4.2. Clinical association/observations

There are no progesterone-specific clinical observations or association reported for lupus pathogenesis, other than that associated with the administration of combination estrogen/progesterone oral contraceptives (82). Much of the supporting data provided for estrogen could only be extrapolated to progesterone with caution. For example, progesterone may be converted to testosterone or estrogen *in vivo* (5). Although medroxyprogesterone is widely administered as a contraceptive agent, its effects on lupus pathogenesis are unclear.

4.3. Epidemiological studies

Female lupus patients have been shown to have, similar to estrogen, abnormally low progesterone concentrations (19,58,71). This is congruent with the pregnancy failure rates in lupus (100) and confirmed by a preliminary study in pregnant SLE patients showing abnormally low progesterone (71), similar to that for estrogen (25).

4.4. Pharmacological administration

There are no double blind, placebo-controlled studies, known to this author, of pure progesterone or anti-progesterone manipulation in lupus patients from which to formulate conclusions regarding progesterone effects on lupus.

4.5. Molecular mechanisms

Perhaps the best evidence for a role for progesterone in lupus pathogenesis comes from its molecular immunomodulatory effects and associations. Progesterone has been shown to increase IL-4 in healthy lymphocytes (86,101). Moreover, during the luteal phase of the menstrual cycle in healthy women, IL-4 in lymphocytes is increased, but this correlated best with estrogen and not progesterone concentrations (91). Obviously, integration of progesterone and estrogen data into their roles in lupus pathogenesis is complex and needs further investigation. At the current time, the relative lack of data precludes conclusions regarding the role of progesterone in lupus pathogenesis.

5. ANDROGENS

Androgens are non-aromatized C-19 steroids primarily produced by the gonads and the adrenals. This portion of the review will be limited to testosterone and dehydroepiandrosterone (DHEA). Testosterone is a gonadal androgen that is aromatizable to 17-beta-estradiol; DHEA is a weaker adrenal androgen that may be

metabolized to progesterone and subsequently to testosterone or estrogen (5). Thus, a major confounding factor regarding the immunosuppressive effects of androgens is their interconversions and aromatization to other steroids.

5.1. Animal studies

Castration of male B/W mice accelerates disease activity (31-33) and administration of androgens (102-104), including DHEA (105), suppresses murine autoimmune disease activity and improves mortality. In these studies however, pharmacological concentrations of androgens were used and their endocrinological and potential pharmacological actions were not assessed. In contrast to estrogen receptor blockade, administration of the androgen receptor blocker, flutamide, accelerated murine lupus (106).

5.2. Clinical observations/associations

The sex ratio of lupus (46), descriptions of gonadal steroid abnormalities in lupus patients with Klinefelter's syndrome (107), and correction of the hypogonadal state with amelioration of disease activity by testosterone in lupus patients with Klinefelter's syndrome (108) have supported the immunosuppressive effects of androgens. There have been no readily available cases of lupus precipitated by male castration or administration of the androgen receptor blocker flutamide.

5.3. Epidemiological observations

Several studies have documented that lupus patients have significantly lower androgens than control patients (56-61,109-111), although its cause and effect status is questioned (112) and suppression of androgens may occur secondary to increased prolactin (12-14). Lahita *et al*. have reported abnormal oxidative metabolism of testosterone in female and male patients, suggesting that this predisposing metabolic change leads to the development of lupus (18). In pregnant SLE patients (25), testosterone concentrations were low compared to controls but did not correlate with disease activity. At the time of this review, there are no published investigations on androgen receptors in SLE.

5.4. Pharmacological administration

Administration of DHEA has been shown to suppress lupus disease activity (113-115), but lupus disease improvement, surprisingly, does not appear to correlate with changes in serum androgen concentrations (116). Unfortunately, administration of DHEA to SLE patients results in a high rate of discontinuation (58% by 12 months) secondary to acne and hirsutism (115), despite its reportedly weak androgenic effects. Direct correlation of DHEA levels to lupus disease activity and its mechanism of action are also confounded by the possibility that DHEA administration to SLE patients not only elevated androgen concentrations (116), but also elevated estrogen concentrations (117). DHEA may also directly stimulate the estrogen response element (ERE)(6). Interestingly, administration of a non-aromatizable androgen, 19-nortestosterone, did not improve SLE in women and worsened it in men (118), suggesting that conversion of androgens to estrogens may be important to their immunosuppressive effects of androgens. As noted above, administration of testosterone to lupus patients with Klinefelter's improves disease activity (108). Danazol, another androgen, is also effective in suppressing lupus disease activity (119) and reversing thrombocytopenia (120).

5.5. Molecular mechanisms

Immunomodulatory effects of androgens are well-documented (83). In addition to the immunodeviation produced by androgens, testosterone (83) and DHEA (121,122) appear to support IL-2 production, a cytokine abnormality reported to occur in SLE (123). Interestingly, DHEA-sulfate has been correlated to IFN-gamma levels *in vivo* (91). Androgens also suppress antibody formation (124), although it is unclear if this is a direct effect on B cells or mediated indirectly through T cells. Experimental, clinical, epidemiological, and pharmacological data within the paradigm of administration or withdrawal/blockade are congruent with the concept that androgens have a significant immunoregulatory role in lupus pathogenesis. Key questions within the context of the pituitary-gonadal axis is whether abnormally low androgen status is primary or secondary to abnormal prolactin responses and does conversion of androgens to estrogens augment their immunosuppressive effect?

6. PROLACTIN

Prolactin is a pituitary peptide hormone that binds to cell surface receptors and mediates nuclear transcription. Its secretion is stimulated by estrogen, blocked by the dopamine agonist bromocriptine, and suppressed by testosterone and progesterone. Its immunostimulatory effects have been previously reviewed (125-130). Prolactin is also produced by lymphocytes and may serve as an autocrine or paracrine factor (131,132). Several animal studies, clinical observations, epidemiological studies, and pharmacological manipulations support the role of prolactin in lupus pathogenesis.

6.1. Animal studies

Prolactin clearly accelerates murine lupus disease activity: increasing serum immunoglobulins and autoantibody levels and accelerating immune complex glomerulonephritis. It does so in both female and male B/W mice (133,134), irrespective of serum estrogen (29,133) or testosterone concentration (134). Conversely, the prolactin suppressive drug, bromocriptine, suppresses murine lupus disease manifestations (29,30,133,135) and prevents estrogen-induced loss of B cell tolerance (30). Although bromocriptine may have direct effects on T and B lymphocytes (136,137), its immunosuppressive effects are reversed by administration of exogenous prolactin (138), suggesting its actions are primarily mediated through suppression of pituitary prolactin (139).

6.2. Clinical observations/associations

Lavalle *et al*. first described abnormalities in prolactin and androgens in male SLE patients (63).

Additional data describing associations between hyperprolactinemia and SLE have been reported (140,141). Case studies have documented direct positive relationships between rising prolactin levels and increasing disease activity and lowered prolactin levels and reduced disease activity (142 and references below).

6.3. Epidemiological and observational studies

Controversy regarding the role of prolactin in lupus pathogenesis has arisen primarily due to studies which found no correlation between prolactin and lupus disease activity or any elevation of prolactin compared to control populations (143-146). However, even in these studies (144-145), an increased percentage (10-15%) of patients with hyperprolactinemia (reviewed in 147) was found. This increased prevalence is 5-7 fold higher than the 2% prevalence of hyperprolactinemia in the general population (148). In further support of an association between prolactin and SLE are a number of studies that demonstrate anomalies in prolactin in association with lupus (20-22,25,149-158). Although one study is contradictory (159), prolactin abnormalities have been extended to pediatric SLE patients (22,160) and include an association with antinuclear antibody formation (161). Walker *et al*. has demonstrated that 20% of premenopausal women with anti-dsDNA were hyperprolactinemic; conversely, 33% of hyperprolactinemic women and 53% of hyperprolactinemic men had antinuclear antibodies (127). In a meta-analyses of all studies with statistical power to detect an association, serum prolactin concentrations were shown to correlate with disease activity (147). Detailed examination of pituitary secretion in SLE patients documents anomalous regulation (162,163); moreover, lupus patients have low levels of homovanillic acid (164), a precursor to dopamine. Lack of dopamine may lead to increased prolactin secretion (10). Anti-prolactin antibodies have been associated with hyperprolactinemia in a preliminary study (165), the significance of this finding is unknown.

6.4. Pharmacological studies

Administration of prolactin precipitated SLE in a RA patient (166) and drugs that increase pituitary prolactin secretion have been associated with drug induced lupus (reviewed in 142). Open-label (167,168) and blinded controlled studies (169,170) document that bromocriptine-induced suppression of prolactin from normal or high concentrations reduces rates of SLE flares or SLE disease activity. In fact, bromocriptine, in a blinded, comparative trial, was found to be as efficacious as hydroxychloroquine in the treatment of SLE (170). Unfortunately, estrogen, progesterone or testosterone were not examined in the course of these initial studies. Bromocriptine suppression of prolactin is typically associated with increased estrogen (15) or androgen (13) concentrations and is used to induce fertility in hyperprolactinemic, amenorrheic women and improves impotency in hyperprolactinemic men (5).

6.5. Molecular mechanisms

Prolactin has several immunomodulatory actions that include, and are not limited to, autocrine and paracrine actions, lymphoproliferation, stimulation of IFN-gamma, and stimulation of antibody and autoantibody formation (171-177). Synovial infiltrating peripheral blood mononuclear cells produce irPRL that can be suppressed by bromocriptine (178). Prolactin can directly stimulate immunoglobulin and autoantibody production by peripheral blood cells (179,180). There may be an immunogenetic predisposition to prolactin abnormalities in patients with lupus or rheumatoid arthritis (181). In the opinion of this author, the majority of studies and the endocrinological paradigm of increased and decreased prolactin associated with autoimmune disease manifestations at all evidentiary strata is most congruent with a significant role for prolactin in lupus pathogenesis.

7. CONCLUSION

The role of sex hormones in the pathogenesis of SLE is complex, interactive, and dynamic. Several contradictory facts challenge traditional concepts of estrogen stimulation of SLE disease pathogenesis. Facts that confound a simple gonadal steroid explanation for the female dichotomy in SLE include: 1) estrogen devoid of its prolactin stimulatory properties in murine lupus models is immunosuppressive, 2) estrogen-receptor blockade or non-aromatizable androgen administration to human lupus patients does not improve and may worsen disease activity, 3) DHEA, an estrogen precursor, increases both estrogen and androgen concentrations and has direct effects on the ERE, 4) estrogen and progesterone are generally low or normal and prolactin is high in SLE patients, 5) androgens are low in SLE, and 6) bromocriptine suppresses lupus disease activity irrespective of estrogen or androgen concentrations. These hormonal anomalies may extend from SLE to other autoimmune diseases. For example, breast feeding or the post-partum period, which is typically characterized by high prolactin and low gonadal steroids (5), has been recently associated not only with flares of SLE (182) but also exacerbations of rheumatoid arthritis (183), and multiple sclerosis (184). Breast-feeding increases stimulated peripheral blood lymphocyte production of all cytokines, but most prominent was IFN-gamma (185). In the opinion of this author, the majority of available data imply that estrogen is suppressive to cell mediated immunity, DHEA/testosterone is suppressive to both cell and humoral mediated immunity, and prolactin is stimulatory to humoral immunity. The data is currently inconclusive regarding the role of progesterone in lupus pathogenesis. An overview of sex hormonal regulation of lupus disease pathogenesis is presented in figure 1 and a summary of the data in this review is presented in Table 3. It is postulated that hypothalamic-pituitary abnormalities (low homovanillic acid/abnormal dopamine metabolism) induce high normal or hyperprolactinemic serum prolactin concentrations at some time during lupus disease development. This leads to inhibition of immunosuppressive gonadal steroid production (estrogen/DHEA), thus facilitating through their absence, immunostimulation, loss of B cell tolerance, autoantibody formation, and clinical disease manifestations. Prolactin also would be directly immunostimulatory to lupus pathogenesis. An alternative hypothesis would be that an initial, abnormal estrogenic surge or insult resets pituitary prolactin thresholds, leading to increased prolactin concentrations, suppression of androgens, and facilitation of lupus disease progression through open “valves”.

Table 3. Relative roles of Sex Hormones in Lupus Pathogenesis

	DHEA	Progesterone	Testosterone	Estrogen	Prolactin
Structure	C-19 steroid	C-21 steroid	C-19 steroid	Aromatized C-19 steroid	Peptide
Origin	Ovary Adrenals	Ovary Adrenal	Ovaries Testes Adipose tissue	Ovary Adipose tissue Contraceptives/replacement therapy Estrogen xenobiotics	Pituitary Lymphocytes
Receptor	Cytosolic	Cytosolic	Cytosolic	Cytosolic	Surface
Receptor action	Nuclear transcription	Nuclear transcription	Nuclear transcription	Nuclear transcription	Signal transduction
Receptor independent actions	Unknown	Unknown	Unknown	Binds to mitotic spindle Binds to surface receptors	Unknown
Regulation	Steroid synthesis precursors and enzymes	Steroid synthesis precursors and enzymes	Steroid synthesis precursors and enzymes	Steroid synthesis precursors and enzymes	Dopamine Homovanillic acid
Immediate precursor	Hydroxypregnenolone	Pregnenolone	Androstenedione Progesterone	Testosterone	Prohormone
Increases induced by	Administration	LH Administration	LH Administration	FSH Ovulatory regimens Administration	Estrogen Testosterone Anti-psychotics
Inhibitor(s)	N/A	RU-486	Flutamide	Tamoxifen Nafoxidine Aromatase inhibitors Cyproterone Buserelin	Bromocriptine
Immune effects	Supports IL-2 production	Supports IL-4 production	Stimulates IL-2 Suppresses antibody formation	Inhibits IL-2 and TNF-alpha Stimulates IFN-gamma & IL-10 Stimulates B cell survival Stimulates antibodies Suppresses T cells	Essential for lymphoproliferation Stimulates IFN-gamma Stimulates antibodies
Significance in lupus	Low in patients with lupus	Low in patients with lupus	Increased oxidation in lupus patients Low in patients with lupus	Increased 16 beta-hydroxylated metabolites Low or normal in patients with lupus	Increased prevalence of Hyperprolactinemia Correlated with disease activity In some studies
Effect in animal model	Suppresses disease	Accelerates disease in pharmacological doses	Suppresses disease in pharmacological doses	Accelerates disease in pharmacological doses Induced genitourinary abnormalities as the cause of death at pharmacological doses Suppresses disease devoid of its prolactin stimulating properties Tamoxifen inhibits disease	Accelerated disease Bromocriptine-induced Suppression of prolactin inhibited disease
Human pharmacological manipulation(s) results	Administration suppresses lupus	Unknown	Non-aromatizable androgen had no effect or worsened lupus Improves lupus in Klinefelter's patients	Oral contraceptives may worsen or improve disease Tamoxifen had no demonstrable effect Cyproterone and buserelin improved lupus disease activity	Suppression of prolactin with bromocriptine reduces disease activity

Further delineation of the hormone and cell specific effects of these major sex hormones should further clarify their relative roles in the pathogenesis of SLE and provide more specific manipulations by hormonal immunotherapy (186). For example, hormonal therapies with estrogen/bromocriptine or DHEA/bromocriptine alone or in combination with traditional agents are theoretical interventions that could be considered.

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