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Hormones and autoimmunity: animal models of arthritis

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Numerous clinical observations implicate hormones in the pathogenesis of a wide variety of rheumatic diseases. For example, the prevalence of systemic lupus erythematosus (SLE) is far higher in females than males (about 9:1), and the incidence of disease in relationship to age increases sharply at puberty, reaches its maximum in the reproductive years (particularly in black females), and then declines markedly in post-menopausal women. Moreover, many clinicians feel strongly that oestrogens exacerbate various aspects of the disease, particularly immune-complex-mediated glomerulonephritis (Wilder, 1995). Rheumatoid arthritis (RA) is similar to SLE in that the prevalence in females is higher than males (3–4:1), but, in contrast, the incidence of disease in relationship to age is very different. The incidence increases steadily from puberty and reaches its maximum at menopause and older age groups. RA is uncommon in males until they reach the age of 45 when the incidence increases substantially and approaches the incidence in females aged 70 and over. In pre-menopausal females, it is not uncommon for the disease to present in the 12 months following a pregnancy, particularly if the mother breast feeds, or for the disease to develop in the period following significant psychosocial stress, which alters the status of numerous hormones. Moreover, pregnancy is often associated with remission, in contrast to SLE, and birth control pills, which hormonally have been considered to induce a pseudopregnant state, offer some degree of diminished risk (Da Silva, 1995; Masi et al, 1995; Wilder, 1995). Observations in animal models of lupus and rheumatoid arthritis also implicate hormones in the pathogenesis of these diseases and provide another perspective in understanding their effects. It is the purpose of this chapter to review briefly current concepts and data addressing the role of hormones in the major animal models of SLE and RA. Major emphasis is on hormones involved in the hypothalamic–pituitary–gonadal and –adrenal axes.

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Gonadal steroid hormones and the hypothalamic–pituitary–gonadal axis

A number of inbred mouse strains spontaneously develop a systemic autoimmune disease resembling human SLE and/or Sjögren's syndrome. These strains include BXSB, MRL-lpr/lpr, NZB, NZW and NZB/NZW F1 mice. Similar to their human counterparts, the incidence and severity of disease in these mouse strains is subject to pronounced gender-related variation (Crofford and Wilder, 1993). The NZB, NZB/NZW F1 and MRL-lpr/lpr strains have younger ages of onset in females, and disease is more severe, whereas the BXSB strain exhibits accelerated disease in males. These gender differences have been attributed to the effects of genes on the X or Y chromosomes, and/or sex hormone differences regulated by the X or Y chromosomes. For example, congenic lupus-prone mice with the X-linked immunodeficiency gene, *XID*, (Rawlings et al, 1993; Thomas et al, 1993), have disrupted B-cell maturation and dramatically prolonged survival (Golding et al, 1983; Nahm et al, 1983; Rosenberg and Steinberg, 1984; Crofford and Wilder, 1993). Ovariectomy decreases severity in NZB, NZB/NZB F1 and MRL-lpr/lpr females, and oestrogen therapy enhances disease severity. In contrast, orchiectomy increases severity in males, whereas testosterone therapy diminishes severity (Homo-Delarch et al, 1991).

Some data on the effects of oestrogen administration on disease expression in MRL-lpr mice, however, suggest more complicated immunomodulatory effects (Carlsten et al, 1990, 1992). Oestrogen therapy in physiological doses increases polyclonal B-cell activation, the production of antibodies to double-stranded DNA, the formation of immune complexes, and accelerates lymphoproliferation, immune complex-mediated glomerulonephritis, renal failure and mortality. In contrast, oestrogen therapy suppresses T-cell dependent lesions, such as focal sialoadenitis, renal vasculitis and periarticular inflammation. Thus, autoimmune disease manifestations in MRL/lpr mice appear to be regulated in a dichotomous fashion by oestrogen. The data suggest that oestrogen promotes B-cell dependent immune function and suppresses T-cell dependent processes. This theme is noted recurrently in the animal model literature and has important implications for evaluating the merits of oestrogen administration in humans.

Immunomodulatory effects, however, do not appear limited to the gonadal steroids such as oestrogen and testosterone. An expanding body of data, in addition, suggest that luteinizing hormone releasing hormone (LHRH) also plays an important role, independently of gonadal steroids, in the pathogenesis of autoimmune diseases (Wilder, 1995). For example, Jacobsen et al (1994) studied intact and castrated lupus-prone SWR × NZB F1 mice and demonstrated that an LHRH-antagonist decreases serum immunoglobulin and anti-DNA levels in castrated male and female mice and improves survival. Treatment with an LHRH agonist exerts reciprocal

effects. These data are important because they support the evolving view that the ontogeny and function of the immune and reproductive systems are intimately linked (Wilder, 1995), i.e. these systems tend to develop and change in parallel. LHRH may provide an additional mechanism to explain this linkage.

Corticosteroids and the hypothalamic–pituitary–adrenal axis

Data also exist that suggest that the development of lupus in MRL-lpr/lpr, NZB, NZW and NZB/NZW F1 mice is enhanced by deficiencies in adrenal corticosteroid production (Chesnokova et al, 1991; Wick et al, 1993). These mice were reported to show age-dependent declines in plasma corticosterone and elevated levels of corticosteroid binding globulin, which would decrease the active fraction of corticosteroid. The mice also have blunted corticosterone production in responses to interleukin (IL)-1 and adrenocorticotrophic hormone (ACTH). Moreover, the development of these hormonal abnormalities, which would be expected to enhance inflammation, parallel the development of autoimmune disease. As expected, corticosteroid therapy of autoimmune MRL-lpr mice clearly suppresses several features of murine lupus. For example, it reduces lymphocytic infiltration in the salivary glands and kidneys and shrinks lymph nodes (Jevnikar et al, 1992).

Prolactin

Prolactin has received considerable attention as a stimulatory factor in human SLE (Jara et al, 1992), as well as murine lupus (McMurray et al, 1991). The major finding is that elevated levels of prolactin appear to exacerbate disease, whereas suppression of prolactin production ameliorates disease. Most of the available data, when considered together, support the view that prolactin stimulates antigen-dependent T-cell development (Wilder, 1995).

In summary, compelling evidence supports the view that several hormones, acting in conjunction with genes on the X and Y chromosomes, play important roles in the pathogenesis of murine lupus. The stimulatory effects of oestrogen and the inhibitory effects of androgens on B-cell dependent immune-complex formation and glomerulonephritis are the most thoroughly documented.

EROSIVE ARTHRITIS MODELS IN MICE

In addition to the spontaneous murine lupus models in which arthritis may be a component, the role of neuroendocrine hormonal factors has also been extensively explored in the collagen-induced arthritis (CIA) model in mice (Crofford and Wilder, 1993). Related studies have been conducted in the CIA model in rats, but some differences are apparent. In particular, the importance and effects of testosterone in mice and rats appear to differ

significantly. Accordingly, the rat and mouse data will be discussed separately.

Gonadal steroid hormones

In mice, collagen-induced arthritis tends to be more severe in males (Holmdahl et al, 1986). As discussed below, the male predominance of CIA is hypothesized to be determined by suppressive effects of oestrogen on disease, genes on the sex chromosomes (particularly polymorphic genes on the X chromosomes), as well as behaviour (fighting amongst males).

Autoreactive B-cells play a critical role in the development of murine CIA, and the autoantibody response is T-cell dependent (Stuart and Dixon, 1983; Helfgott et al, 1984; Ranges et al, 1985). An impressive body of work has been published supporting the view that oestrogen suppresses murine CIA. Oophorectomy enhances susceptibility, whereas oestrogen treatment that maintains physiological levels protects against the development and perpetuation of arthritis, suppresses anti-type II collagen T-cell immunity, but, interestingly, this treatment stimulates polyclonal B-cell activity (Holmdahl et al, 1986; Jansson et al, 1990). Oestrogen administration also suppresses arthritis severity in both castrated and non-castrated males, indicating that its effects are independent of testosterone (Jansson and Holmdahl, 1992). Similar to humans with rheumatoid arthritis, pregnancy suppresses CIA in mice, and arthritis exacerbates postpartum. Oestrogen therapy maintaining pregnancy levels can strikingly suppress the postpartum flare. Progesterone, in the postpartum period, adds to, but does not replace, the disease suppressive effects of oestrogens (Jansson and Holmdahl, 1989; Mattsson et al, 1991). Since erosive disease in CIA is clearly dependent upon intact T-cell function, these data, like the murine lupus data, imply that oestrogens have dichotomous effects. They suppress T-cell dependent immune functions, but stimulate T-cell independent, B-cell dependent humoral immunity.

The effects of testosterone in murine CIA are complicated (Carlsten et al, 1989). Some of the earliest data in murine autoimmune disease suggested that testosterone suppresses measurable parameters of antigen-specific immunity including both delayed type hypersensitivity (DTH) and antibody responses (Raveche et al, 1976). In murine CIA, testosterone administration has either no effects or enhances disease. In contrast to oestrogen, it enhances disease only in normal but not castrated mice. This observation suggests that testosterone enhances disease, in both sexes, because it suppresses oestrogen production (Jansson and Holmdahl, 1992). Testosterone also affects behaviour in male mice in that it promotes fighting, which also tends to worsen disease severity (Holmdahl et al, 1992). All of these factors complicate the interpretation of testosterone's effects in murine CIA arthritis.

Although the effects of testosterone in CIA are complex and difficult to interpret, some of the complexity may ultimately be resolved in the context of studies addressing the role of the X and Y chromosomes on CIA. For example, the androgen receptor is critical in regulating the effects and

sensitivity to testosterone, and the androgen receptor gene is located on the X chromosome (Cohn, 1979; Cerry et al, 1989). The steroid sulphatase gene is also located on the X chromosome, and this enzyme is clearly important in regulating the activity of testosterone and other androgens (Crocker and Craig, 1983; Keitges et al, 1987). These observations are clearly relevant because reciprocal F1 breeding studies have demonstrated that genes regulating murine CIA do, in fact, reside on the X chromosome. To date, the only gene located on the X chromosome that has been shown to affect CIA is the *XID* gene, which encodes a defective B-cell specific tyrosine kinase called *btk* (Rawlings et al, 1993; Thomas et al, 1993). The presence of this defective gene in an otherwise CIA-prone mouse strain ameliorates the development of CIA (Jansson and Holmdahl, 1993). Genes on the Y chromosome may also affect disease. For example, the *Yaa* ('Y autoimmune accelerating') gene has been shown to affect the development of several autoimmune diseases. In BXSB lupus mice, this gene accelerates disease through interactions with genes on the X chromosome. The *XID* defect inhibits or delays the effects of the *Yaa*-linked disease in lupus-prone mice (Golding et al, 1983). Interestingly, the *Yaa* gene suppresses CIA in mice (Jansson and Holmdahl, 1994). Numerous other genes also reside on the X chromosome and may play a role in arthritis. For example, the gene for *TIMP*, the tissue inhibitor of metalloproteinases, is located on the X chromosome (Jackson et al, 1987). This inhibitor limits metalloproteinase activity in erosive joint disease, but no data exist to indicate that polymorphisms in this gene regulate arthritis expression. Hormonal effects on the expression of this gene are unknown.

Prolactin, melatonin and pineal gland

The effects of prolactin, like murine lupus, have also been investigated in murine CIA. In DBA/1 mice, prolactin injections make CIA arthritis worse if treatment is performed during the induction of disease. Treatment in later stages of disease has no effect (Mattsson et al, 1992).

Melatonin, a hormone produced by the pineal gland, has a well known role in control of reproduction ('seasonal breeding') in many mammalian species. It also affects thermoregulation, sleep, pituitary function, adrenocortical function and thyroid function. In addition, it affects the growth of cancer cells and lymphoid cells, enhances T-cell dependent humoral immune responses, and regulates natural killer cell activity. It has been hypothesized that it may work by enhancing pituitary prolactin release and/or endogenous opiates. This information is interesting in the context of a study showing that constant darkness enhances autoimmunity to type II collagen (CII) and exaggerates development of collagen-induced arthritis in DBA mice, independently of sex steroids. This effect appears to be secondary to enhanced release of melatonin. Animals raised in constant light have more severe arthritis when injected with melatonin from days 1 to 10 but not if injected at day 10 (Hansson et al, 1992). Moreover, pinealectomy ameliorates disease severity (Hansson et al, 1993).

EROSIVE ARTHRITIS MODELS IN RATS

The collagen-induced arthritis model is studied extensively in both mice and rats. In fact, rats tend to be more susceptible than mice to CIA arthritis in that disease can, in many circumstances, be induced with type II collagen emulsified in incomplete Freund's adjuvant, instead of complete Freund's adjuvant. In addition to the CIA model, several other models of erosive arthritis are inducible in genetically-susceptible rats including streptococcal arthritis and other forms of bacterial cell wall-induced arthritis, adjuvant arthritis and avridine arthritis (Crofford and Wilder, 1993; Holmdahl, 1995). Mice tend to be relatively resistant to induction of arthritis with bacterial cell walls and are resistant to adjuvant and avridine arthritis. The role of hormones in these T-cell dependent arthritis models has been a focus of interest for many years.

Gonadal steroids

As stated previously, male mice tend to have more severe CIA than females, but, depending on the inbred strain and the type of collagen, the opposite is generally true in rats. For example, DA and Lewis female rats are both susceptible to homologous type II collagen arthritis, but females develop earlier onset disease and have a more severe course. The sex differences are more striking in Lewis rats (Holmdahl, 1995). DA males and females are similarly susceptible to heterologous type II collagen arthritis, but DA×BN F1 females are more susceptible than males (Griffiths and DeWitt, 1984). Females of several strains, such as Lewis, develop more severe streptococcal cell wall arthritis than males (Wilder et al, 1982; Allen et al, 1983). In some strains of rats selectively bred for adjuvant arthritis, females are more susceptible than males (Mackenzie et al, 1979). Other strains do not show a difference in males and females for adjuvant arthritis (Perlik and Zidek, 1973). DA and Lewis rats are both susceptible to avridine arthritis, but females have earlier onset of disease than males (Holmdahl, 1995).

The mechanisms underlying the tendency for earlier onset of arthritis in females and a more severe course have been subject to several investigations. As noted in mice, oestrogen suppresses rat CIA arthritis, without suppressing anti-type II collagen antibody responses (Larsson and Holmdahl, 1987). However, an important difference in the action of testosterone appears to exist between rats and mice. For example, to address the possibility that sex chromosomes are involved in the gender differences in DA and Lewis rats, Holmdahl (1995) studied reciprocal F1 crosses of DA×LEW and LEW×DA. Female DA×LEW F1 rats are more susceptible than males, but LEW×DA F1 rats do not show a sex difference. The difference is most apparent in intact rats. Castration of the male DA×LEW F1s eliminates the sex difference indicating the protection of males is influenced by sex steroids. Both oestrogen and testosterone, in contrast to what is noted in mice, have a suppressive effect on the disease. These data indicate that sex chromosomes (Y from Lewis or X from DA)

regulate disease susceptibility, but the suppressive effects of the X chromosome from DA or the Y chromosome from Lewis are dependent upon sex hormones. Both oestrogen and testosterone are suppressive, but testosterone's suppressive effects, in contrast to mice, appear to be more important than those of oestrogen. Testosterone also appears to be important in the development of more severe streptococcal cell wall arthritis in female compared to male Lewis rats (Wilder et al, 1982; Allen et al, 1983). Castrated males or intact males treated with oestrogen develop disease similar in severity to females. The effects of oestrogen administration were only studied in normal and were not studied in castrated males. It appears, therefore, possible that the enhancing effects of oestrogens in the male rats is a consequence of disrupting testosterone production in the male Lewis rats (Allen et al, 1983). Considered together, the data suggest that polymorphic genes on the X, and, to a lesser extent, the Y chromosomes regulate the gender differences in susceptibility and severity, but the effects of these genes are mediated, in part, by the arthritis suppressive actions of both oestrogen and testosterone. Testosterone appears to be the more potent inhibitor in rats, whereas in mice, oestrogen appears to be the more potent inhibitor.

Corticosteroids and the hypothalamic–pituitary–adrenal axis

Corticosteroids are the most potent natural anti-inflammatory agents known. They also have diverse immunomodulatory activities relevant to erosive inflammatory arthritis (Sternberg and Wilder, 1993). Compelling data from studies on Lewis inbred rats indicate that corticosteroids and the hypothalamic–pituitary–adrenal axis play an important role in autoimmune diseases including erosive arthritis. Lewis rats, particularly females, are susceptible to a diverse array of experimentally-induced autoimmune inflammatory diseases, particularly T-cell dependent diseases (Wilder, 1995). For example, these rats develop severe streptococcal and other forms of bacterial cell wall arthritis. They are also highly susceptible to type II collagen arthritis, adjuvant arthritis and avridine arthritis (Holmdahl, 1995). They are widely used in studies of experimental allergic encephalomyelitis (EAE) and experimental autoimmune uveitis (EAU) (Wilder, 1995). In contrast, inbred rat strains such F344 are relatively resistant to these diseases, although F344 inbred rats are histocompatible with Lewis rats at major histocompatibility complex (MHC) class II loci. They do differ, however, at MHC class I loci (Wilder et al, unpublished data).

Lewis rats, compared to F344 inbred rats, have a profound defect in their stress response system, particularly the hypothalamic–pituitary–adrenal axis (Sternberg et al, 1989a,b; Wilder, 1993, 1995). Under basal conditions, Lewis rats, compared to F344 rats, have lower plasma corticosteroid levels and blunted circadian variation (Griffin and Whitacre, 1991; Dhabhar et al, 1993). In response to diverse stimuli (streptococcal cell walls, lipopolysaccharide (LPS), interleukin-1, various neurotransmitters, corticotrophin releasing hormone (CRH), snake venom, and various environmental stressors), Lewis rats produce substantially less pituitary ACTH and adrenal

corticosterone than F344 rats (Sternberg et al, 1989a,b; Calogero et al, 1992; Sternberg et al, 1992; Smith et al, 1994; Spinedi et al, 1994). Lewis and F344 rats have similar pituitary ACTH responses to arginine vasopressin (AVP), angiotensin II, insulin, ether, or adrenalectomy, which can activate pituitary corticotrope responses independently of hypothalamic CRH (Spinedi et al, 1994; Chisari et al, 1995). Lewis rats also have smaller adrenal and pituitary glands than F344 rats (Sternberg et al, 1989a), and pituitary corticotrope numbers and responses to CRH are blunted (Zelazowski et al, 1992). These data suggest that the primary abnormality in Lewis rats involves the hypothalamus resulting in defective CRH production. In fact, blunted CRH production has been directly demonstrated (Sternberg et al, 1989b, Calogero et al, 1992). More recently, Smith et al (1994) examined hypothalamic PGE2 and cAMP production and adrenocortical production of corticosterone in Lewis and F344 rats in response to intraperitoneal injection of endotoxin. They noted, as have other investigators, that F344 rats have higher corticosterone responses to LPS than Lewis, but they also demonstrated that Lewis rats have greater increases in PGE2 and cAMP in hypothalamus than F344 rats. They also noted that basal levels of PGE2 and cAMP are higher Lewis than F344 rats. The corticosterone responses were blocked by indomethacin, indicating that PGE2 production is involved in the activation of the HPA axis response. More importantly, the data imply that the hypothalamic CRH neuron in Lewis versus F344 rats is insensitive to stimulatory factors. These data are compatible with similar conclusions reached by Calogero et al (1992).

AVP, like CRH, is also a hypothalamic secretogogue for pituitary ACTH. In light of the defective production of hypothalamic CRH in the Lewis rat and blunted CRH-mediated pituitary–adrenal responses, AVP status has been investigated in these strains. Although there is some disagreement regarding AVP content in the hypothalamus (Patchev et al, 1992; Spinedi et al, 1994), all investigators agree that AVP responsiveness in Lewis is intact compared to F344 rats. In fact, Lewis rats have higher plasma levels of AVP than F344 rats. The maintained AVP responsiveness probably explains the equivalent pituitary ACTH responses to ether, insulin, angiotensin II and adrenalectomy in Lewis and F344 rats. These agents stimulate both CRH and AVP, while inflammatory mediators such as endotoxin and IL-1 stimulate CRH but not AVP (Spinedi et al, 1994). The enhanced production of AVP by Lewis rats may participate in their susceptibility to inflammatory disease because AVP appears to have pro-inflammatory actions (Patchev et al, 1993).

The precise molecular basis for the genetically-determined HPA axis abnormalities in Lewis rats is not clear. Some investigators have implicated abnormalities in the corticosteroid receptor levels (Dhabhar et al, 1993), but it appears likely that the abnormalities have a complex multifactorial basis. Ongoing genetic linkage analysis in F2 progeny of Lewis and F344 rats indicates that arthritis susceptibility is regulated for at least three, and probably more genetic loci (Wilder et al, unpublished data). Nevertheless, it appears clear that HPA axis hyporesponsivenes in Lewis rats plays a role in the susceptibility of Lewis rats to autoimmune inflammatory diseases

and resistance of F344 rats. Treating Lewis rats very early with physiological range corticosteroids profoundly inhibits the development of streptococcal cell wall arthritis and most other autoimmune diseases, whereas blocking the effects of corticosteroids with RU486 in F344 rats precipitates severe, potentially lethal, acute inflammation, including arthritis. Corticosteroids clearly have profound anti-inflammatory effects in these two inbred rat strains.

An interesting aspect of HPA axis studies, relevant to the experimental arthritis models, is that HPA axis responsiveness is sexually dimorphic. Female rats, both Lewis and F344, have higher plasma ACTH and corticosterone levels, both basally and in response to most stressors, than male rats (Griffin and Whitacre, 1991; Spinedi et al, 1994; Chisari et al, 1995). Female Balb/c mice also have higher basal level of plasma corticosterone than males, and the HPA axis response to different stress stimuli is significantly higher in female than in male mice. These sex differences can be eliminated by gonadectomy alone or re-established in females with oestrogen replacement therapy (Spinedi et al, 1992). Thus, HPA axis responsiveness is linked to gender and the gonadal steroid environment. This sexually dimorphic HPA axis responsiveness may reflect direct regulation of the CRH gene by oestrogen. The promoter region of the CRH gene contains oestrogenic responsive elements (Vamvakopoulos and Chrousos, 1993). These observations emphasize the close interrelationships of the hypothalamic–pituitary–adrenal and –gonadal axes and suggest further avenues for sexually dimorphic expressions of autoimmune inflammatory arthritis.

Peripheral CRH

In the course of investigating CRH, data were generated indicating the CRH is actually secreted locally in inflammatory sites where it appears to have a pro-inflammatory action (Karalis et al, 1991; Wilder, 1995). Subsequently, CRH expression was investigated in the joints of Lewis rats with streptococcal or adjuvant arthritis compared to joints of arthritis-resistant F344 rats. Interestingly, high level expression of CRH was noted in the joints of Lewis rats with arthritis but not in the joints of F344 rats. In other words, autoimmune-arthritis prone Lewis rats express CRH in peripheral inflammatory sites but have defective hypothalamic expression of CRH. Arthritis-resistant F344 rats express CRH in an antithetical pattern, i.e. high levels in the hypothalamus, but low levels in the joint (Crofford et al, 1992). These data suggest that the nervous, endocrine, immune and inflammatory systems are intimately linked and that CRH, like LHRH, may play a critical role integrating these systems. These peripheral CRH data are also relevant to human disease. For example, high level CRH expression has been demonstrated in synovial tissues and fluids from patients with rheumatoid arthritis (Crofford et al, 1993), a pattern highly reminiscent of the Lewis rat. Although CRH expression has not been measured in the hypothalamus of patients with RA, these observations suggest that hypothalamic CRH expression may be defective in RA

patients, similar to Lewis rats. Defective HPA axis responses to inflammatory mediators have been reported in RA patients (Chikanza et al, 1992).

Prolactin

Prolactin has been the subject of interest not only in the context of SLE and the murine models of lupus, but also rheumatoid arthritis and adjuvant model. Similar to the lupus models, prolactin excess appears to enhance disease severity, and deficiency blunts disease (Berczi and Nagy, 1985; Berczi et al, 1993).

SUMMARY

Hormones, particularly those involved in the hypothalamic–pituitary–gonadal and –adrenal axes (HPG and HPA), play important roles in various animal models of autoimmunity such as systemic lupus erythematosus in mice and collagen-induced arthritis (CIA) in mice and rats, and the streptococcal cell wall, adjuvant and avridine arthritis models in rats. Intimately linked to the subject of hormones and autoimmunity are gender, sex chromosomes and age. The importance of these factors in the various animal models is emphasized in this chapter. Several major themes are apparent. First, oestrogens promote B-cell dependent immune-complex mediated disease (e.g. lupus nephritis) but suppress T-cell dependent pathology (CIA in mice and rats), and vice versa. Second, testosterone's effects are complicated and depend on species and disease model. In rats, testosterone suppresses both T-cell and B-cell immunity. In mice, the effects are complex and difficult to interpret, e.g. they tend to enhance CIA arthritis and suppress lupus. Sex chromosome/sex hormone interactions are clearly involved in generating these complicated effects. Third, studies in Lewis and Fischer F344 rats exemplify the importance of corticosteroids, corticotrophin releasing hormone and the HPA axis in the regulation of inflammation and the predisposition to autoimmune diseases. Fourth, the HPA axis is intimately linked to the HPG axis and is sexually dimorphic. Oestrogens stimulate higher corticosteroid responses in females. The animal model data have major implications for understanding autoimmunity in humans. In particular, adrenal and gonadal hormone deficiency is likely to facilitate T-cell dependent diseases like rheumatoid arthritis, while high oestrogen levels or effects, relative to testosterone, are likely to promote B-cell dependent immune-complex-mediated diseases such as lupus nephritis.

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