Hormone and immune system interactions in demyelinating disease

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Abstract

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The immune, endocrine and nervous systems communicate with each other through a myriad of molecules including cytokines, hormones and neurotransmitters. Alterations in the balance of the products of these systems affect susceptibility to autoimmune disease and also the progression of disease. One of the most intensely studied autoimmune diseases is multiple sclerosis (MS). The purpose of this review is to explore the relationships between sex hormones and MS disease progression and to attempt to understand the paradox that although women are more likely to develop MS, female sex hormones appear to be beneficial in symptom amelioration. The proposed mechanisms of the therapeutic action of estrogens will be discussed with respect to T cell polarization and also on CNS cell populations. Investigations into the pathogenesis of multiple sclerosis (MS) and animal models of MS have given insights into the interactions between the neuroendocrine systems and provide important potential therapeutic venues that may be expanded to other autoimmune and neurodegenerative conditions.

Introduction

Multiple sclerosis (MS) — epidemiology and pathogenesis

Multiple sclerosis is the most common demyelinating disease of the central nervous system (CNS) occurring at an incidence of approximately 350,000 in the United States and 2.5 million worldwide (Anderson et al., 1992; Compston and Coles, 2002; Noonan et al., 2002). The total average costs are greater than $47,000 per patient per year once medical and non-medical costs, production losses, and informal care are taken into consideration (Kobelt et al., 2006). MS is characterized by acute, focal demyelination and neurodegeneration of the CNS. Pathologically, the hallmark of MS is the plaque, occurring in the white matter of the CNS, usually in a perivascular fashion around post-capillary venules. The lesions are thought to result from immune-mediated destruction of...
myelin (Noseworthy et al., 2000; Wingerchuk et al., 2001). Characterization of perivascular infiltrate within the active MS plaque has identified activated macrophages, T cells, and some plasma cells which are thought to contribute to the pathology (Lucchetti et al., 2000). The symptoms of MS reflect its pathological changes, and may include, but are not limited to; optic neuritis, clumsiness, gait ataxia, limb weakness, paralysis, cognitive impairment, sexual dysfunction, fatigue, pain, incontinence, and depression (Noseworthy et al., 2000).

The onset of MS typically occurs between the ages of 15 and 40, usually followed by a relapsing remitting course, in which the patient experiences an acute relapse that lasts 24 h or longer, but that is followed by remission which may last months or years (Kantarci and Weinshenker, 2005). Eventually most patients will develop the secondary progressive form of the disease. The transition to secondary progressive MS, while not yet completely understood, is thought to be mediated in part by accumulative neurodegeneration and cerebral atrophy (Kantarci and Weinshenker, 2005). In more than 85% of all cases, MS presents as a progressive and debilitating disease requiring the use of a walking aid within 15 years after onset (Weinshenker et al., 1989). Approximately 20% of patients with MS develop a chronic progressive form of the disease from the onset. Even though MS is rarely a direct cause of death, increased suicide rates have been associated with this disease, thus making it a cause of premature death (Goldman consensus group, 2005).

Hormones and autoimmunity

Generally speaking, autoimmune diseases are more common in women than men with notable exceptions of autoimmune diseases of the kidney: post-streptococcal glomerulonephritis, Henoch–Schönlein purpura, IgA nephropathy, Goodpasture’s syndrome and membranous nephropathy (Beeson, 1994). The most female sex-biased disease is Sjögren’s syndrome with 95% of patients being women and the closely-related disease: systemic lupus erythematosus (SLE) where 85% of the patients are women. Examining autoimmune diseases that affect men more commonly, the most male biased disease is thromboaegitis obliterans with 95% male and a close second is Goodpasture’s syndrome with 85% males affected.

Sex bias in multiple sclerosis

For the purposes of this review we will focus on multiple sclerosis, the most common autoimmune disease of the CNS. Multiple sclerosis occurs 2–3 times more frequently in females (Whitacre, 2001) and interestingly this female preponderance has been shown to have increased to 4:1 in a recent Canadian study (Orton et al., 2006). The increased prevalence of MS in women occurs irrespective of racial ethnicity (Confavreux et al., 1998). However, there is an interesting apparent contradiction with regard to hormones and MS. Although being female is a risk factor for MS, female hormones appear to play a role in improving the symptoms of established MS.

The principal hormones that have been investigated in experimental models of MS are the estrogens; namely, 17-β-estradiol and estriol. While estradiol plays several roles in the body and it can be found in both males and females with much higher levels found in females, estriol increases to high levels only during pregnancy and especially during the third trimester. As such, estriol is commonly referred to as a hormone of late pregnancy since it is produced by the fetal-placental unit (Sicotte et al., 2002).

Hormones may have beneficial effects on autoimmune disease through various mechanisms: by modulating the immune system and/or affecting the target organ. Sex hormones are known to have an impact on the development of the immune response. For instance pregnancy affects the immune system shifting responses from T helper 1 (Th1) toward Th2 which could account for the disease remission seen in MS during pregnancy (Confavreux et al., 1998). Following vaccination, females produce more antibodies and they have an increased level of T-cell activation (Whitacre, 2001). In humans, studies the only noticeable difference is that females have an increased number of CD4+ lymphocytes but not necessarily increased levels of antibody or cytokines following vaccination (Whitacre, 2001). Female hormones modulate the immune response and have been shown to dampen the Th1 response (Voskuhl, 2003; Whitacre, 2001). For Th1-mediated diseases such as MS and rheumatoid arthritis (RA), this may explain the disease suppressing effects of pregnancy. In contrast typical Th2-mediated diseases, such as SLE, are exacerbated by pregnancy (Whitacre, 2001). However, it is important to note that antibodies also play a pathogenic role in MS (Srivastava et al., 2012) and so a Th1 to Th2 switch as an explanation for therapeutic actions of sex hormones maybe too simplistic.

Hormone treatments in animal models of MS

Animal models of autoimmunity have provided insights into the mechanisms of action of hormones on autoimmune diseases. In the case of MS, there are two main types of animal models: experimental autoimmune encephalomyelitis (EAE) and virus-induced demyelination. EAE involves generating autoactivity to myelin components and is useful for studying the autoimmune aspects of MS as well as trafficking of myelin reactive cells into the CNS from the periphery. For the purposes of this review we will consider the role of hormones in EAE and one of the most researched viral models of MS: Theiler’s virus-induced demyelination (TVID).

EAE and T cell subsets

By analogy with EAE, the symptoms of MS were thought to arise as a result of activation of the T cell subset: Th1. However, recent experiments in EAE have demonstrated that Th17 cells contribute greatly to the pathogenesis of EAE. T cell subsets are classified depending on their transcription factors and cytokine secretion patterns summarized below. Th17 helper cell subset has also been implicated in several other experimental models of autoimmunity, and most importantly in MS (Witowski et al., 2004).

Th1 and Th2 T cells

Since the 1980s a dichotomous paradigm has been used to explain the nature of immunity (Abbas et al., 1996), such that T helper type 1 (Th1) responses are generated to combat intracellular infections, whereas type 2 responses facilitate the generation of humoral immunity to combat extracellular infections. While innate immune cells, particularly professional antigen presenting cells (APC) such as dendritic cells and macrophages, play a vital role in the generation of the different types of immune responses, CD4+ T helper (Th) cells orchestrate the immune response. As such, Th1 cells have been associated with cell-mediated anti-viral immunity, whereas Th2 cells have been depicted as generating humoral immunity through the stimulation of B cells. Additionally, the cytokines produced by these T cell subsets are antagonistic to each; Th1 cells producing IFN-γ which downregulates Th2 cells and Th1 cells produced IL-4 and IL-10 which downregulate Th2 cells (Fig. 1). The polarization of naïve (Th0) CD4+ T cells into effector cells requires presentation on major histocompatibility complex (MHC) class II antigen by a professional APC, recognition of the antigen by the T-cell receptor, and co-stimulation via binding of CD28/80 to B7-2, LFA1/ICAM-1 and CD40/CD40L. Additionally, the polarization of Th1 cells requires the binding of IL-12 and IFN-γ to their receptors on the Th0 cell, subsequent phosphorylation of the signal transducer and activator of transcription (STAT) 4 and STAT1, respectively, and ultimately the activation of the transcription factor T-bet (Szabo et al., 2000). While NK cells and CD8+ T cells can also secrete IFN-γ, this cytokine is recognized as the prototypical hallmark of Th1 polarization (Abbas et
S100A9, S100A7, and S100A8 (Liang et al., 2006). Moreover, this protective role in EAE through immunoregulatory cytokine production in CD4+ T cells has been demonstrated to be both necessary and sufficient for Th2 polarization (Zhang and Flavell, 1997). Th2 cells secrete the interleukins: IL-4, IL-5, IL-10 and IL-13.

Th17 cells

While Th1 and Th2 immunity are influenced by the functions of IL-12 and IL-4 respectively, the generation of Th17 cells requires the synergistic effects of IL-6 and TGF-β as well as the aid of TNF-α and IL-1β (Bettelli et al., 2006; Mangan et al., 2006; Veldhoen et al., 2006). Following the initial polarization of these cell types, their survival and propagation are dependent on the actions of IL-23 (Aggarwal et al., 2003; Harrington et al., 2005; Sutton et al., 2006). The stimulation of Th6 cells within this inflammatory milieu has been shown to activate the orphan nuclear transcription factor ROR-γt (Ivanov et al., 2006). In mice this transcription factor takes on the role of T-bet and GATA-3 in Th1 and Th2 polarization respectively, insofar as ectopic expression will result in Th17 polarization (Ivanov et al., 2006). Interestingly, Veldhoen et al. (2006) demonstrated that a lack of IFN-γ, IL-12/23 or IL-4 without TGF-β1 production can also drive Th17 cell responses. While the effector function of Th17 cells is still in the process of being characterized, these cells have been shown to mediate protection against extracellular bacteria (Happe et al., 2005; Mangan et al., 2006). Also, IL-17 has recently been demonstrated to enhance the expression of the antimicrobial peptides β-defensin 2, S100A9, S100A7, and S100A8 (Liang et al., 2006). Moreover, this protection may be brought about by the functions of IL-17 and IL-22, the cytokines secreted by Th17 cells (Harrington et al., 2005; Liang et al., 2006; Park et al., 2005). For instance, IL-17 increases in both KC and G-CSF resulting in neutrophilia (reviewed by Kawaguchi et al., 2004; and Witowski et al., 2004).

MS has for a long time been considered a Th1-mediated autoimmune disease (Sospedra and Martin, 2005). However, Th17 responses have taken center stage as these cells, but not the previously implicated Th1 cells, have been shown to be crucial for the generation of experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis, and experimental autoimmune myocarditis, rheumatoid arthritis, and autoimmune myocarditis (Bettelli et al., 2006; Cua et al., 2003; Chen et al., 2006; Komiyama et al., 2006; Sutton et al., 2006; Rangachari et al., 2006). In human MS, it has been shown recently that patients have increased IL-17 mRNA expression in the brain and cerebral spinal fluid (Witowski et al., 2004). Additionally, Valnik-Dembinsky et al., 2006 have demonstrated that IL-23 is increased in dendritic cells isolated from MS patients, and that isolated CD4 T cells stimulated with anti-CD3 antibodies produce more IL-17 than healthy controls.

**Regulatory T cells**

CD4+ CD25+ Foxp3+ T regulatory cells make up approximately 10% of peripheral CD4+ T cells in mice and humans. T reg are non-responsive in vitro and possess the ability to suppress other T cells mainly via the production of immunosuppressive cytokines (reviewed in Thompson and Powrie, 2004). Interestingly, deletion of FoxP3 results in spontaneous autoimmunity (Kim et al., 2007). Decreased numbers of regulatory T cells have been reported in MS patients (Vigilletta et al., 2004). Enhanced FoxP3 expression and T reg cell function have been reported in both pregnant and estrogen-treated mice (Polanczyk et al., 2005). Thus, one of the mechanisms of the therapeutic actions of estrogen may be via enhancing T regs.

**Estrogen treatment in EAE**

Early studies with EAE in SJ mice revealed a similar sex bias to that seen in MS (Bebo et al., 1996, 1998, 1999 and Voskuhl et al., 1996). In addition, androgens have been shown to have a protective role in EAE (Palazynski et al., 2004a). However, there are some strains of mice, B10.PL and PL/J where the males are more susceptible to EAE (Papenfuss, et al., 2004) and in C57BL/6 mice there are no sex differences (Okuda et al., 2002). Therefore other genes are involved and the reason for sex differences is more complicated than originally thought.

The role of estrogen and estrogen receptor agonists has been further investigated in EAE (Bebo et al., 2001; Morales et al., 2006; Tiwari-Woodruff et al., 2007). Experimentally, 17β estradiol has been shown to reduce EAE in mice by inhibiting both encephalitogenic T cells and cell migration into the CNS and increasing the activity of CD4+ CD25+ regulatory T cells (Offner and Polanczyk, 2006). 17β estradiol has also been shown to promote axon and myelin survival (Offner and Polanczyk, 2006). Interestingly, pregnancy also plays a protective role in EAE through immunoregulatory cytokine production in particular, increases in IL-10 and decreases in IL-17, TNF-α reductions (McClain et al., 2007).

In the EAE model, females that were ovariectomized but not treated with hormone replacement therapy, did not show altered disease severity when compared to placebo-treated non-ovariectomized mice. This indicates that physiological levels of estrogens may not be enough to cause any effect on disease progression in this model once the disease has begun (Voskahl and Palazynski, 2001). Conflicting results were shown if treatment with physiologic levels of estradiol and estriol was administered prior to the onset of EAE (Bebo et al., 2001). Nevertheless, estriol has been shown to be protective in studies with human MS patients and in the non-ovariectomized EAE model of MS (Palazynski et al., 2004b; Sicotte et al., 2002; Spence and Voskuhl, 2012).

Progesterone treatments in intact female C57BL/6 EAE mouse models have shown that treatment with pregnancy level progesterone led to an attenuation of symptoms and increased levels of protective cytokines, notably interleukin-10 (IL-10) (Garay et al., 2007; Yates et al., 2010).

**Effect of chromosomal sex on autoimmunity**

Hormones appear to play a role in sexual dimorphism seen in autoimmune diseases but chromosomal sex also has an effect. In a recent study by Smith-Bouvier et al., they examined the influence of chromosomal sex on the susceptibility to autoimmune diseases: MS and SLE. The group tested this hypothesis using XX and YY-deficient XY female mice and XX-Sry and XY Sry male mice that were gonadectomized to examine the effects of chromosome complement without any sex...
hormones (Smith-Bouvier et al., 2008). They found that XX sex chromosome complement rendered SJL mice more susceptible to both experimental autoimmune encephalomyelitis (EAE) and the pristane-induced lupus model (Smith-Bouvier et al., 2008). In addition, the immune response is altered by XX complement, with XY females producing anti-inflammatory Th2 cytokines such as IL-13 and IL-5 (Smith-Bouvier et al., 2008). This may help explain why females may be more susceptible to autoimmune diseases, and why they are more often afflicted.

The effects of estrogens in the CNS

Astrocytes are essential components of the blood–brain barrier (BBB), and they are important in cell-to-cell communication, not only with cells in the CNS, but also with inflammatory cells (Kipp and Beyer, 2009). Estradiol has been shown to prevent astrocytes from expressing MHC-II and to enhance the induction of T-cell apoptosis (Kipp and Beyer, 2009). Expression of ERα is necessary in astrocytes to prevent axonal loss, gliosis, and diminish or prevent lymphocyte and monocyte infiltration into the CNS (Spence et al., 2011). Additionally, estradiol has positive effects on brain circulation and in young animal models, reduces stroke severity (Cipolla et al., 2009; Selvamani and Sohrabji, 2010). The reduction in stroke severity is due to estradiol’s influence on the BBB, at the level of both endothelial cells and astrocytes. During stroke, edema causes damage to the parenchyma. Cipolla et al. (2009) found that ovariectomy in rats increases BBB permeability, but that treatment with estradiol/estriol combination therapy restores the integrity of the barrier almost to control level. The levels of estradiol found in this study are almost at the levels found at estrus in the rat ovarian cycle (Shalik, 1971), making them a comparable measure to the dose of estradiol given in this study.

Both estriol and estradiol can bind to estrogen receptors α and β (ERα and ERβ, respectively). However, estradiol has a higher affinity for ERβ while estriol has a higher affinity for ERα (Spence and Voskuhl, 2012). ERα has been implicated in EAE as having a potent anti-inflammatory response. Binding of estradiol to ERα inhibits the transport of the pro-inflammatory transcription factor NF-κB into the nucleus via interaction with PI3K, most notably in microglia, the resident macrophages of the CNS (Spence et al., 2011; Vegeto et al., 2008). In ischemia, ERα-mediated suppression of these cells and other inflammatory cells seems to be responsible for neuroprotection in young female rats post-stroke (Selvamani and Sohrabji, 2010). In vitro experiments have shown that stimulation of ERα by estradiol, or estril agonists, suppresses transcription of NF-κB in astrocytes and thereby decreases the TNF-α-mediated production of the pro-inflammatory chemokine CCL2 (Giraud et al., 2010). This reduced levels of CCL2 then resulted in inhibiting the infiltration of peripheral lymphocytes into the CNS (Spence and Voskuhl, 2012). ERβ stimulation did not have this effect. In addition, treatment with ERα ligand reduced spinal cord inflammation, whereas ERβ ligand treatment only showed protective effects in the long term, but no reduction in inflammation (Tiwari-Woodruff and Voskuhl, 2009). One final observation is that estradiol increases the ability of astrocytes to resorb excess glutamate, thus preventing neuronal loss due to excitotoxicity and explaining the relative effectiveness of estradiol versus estriol’s therapeutic effects on treated mice (Spence and Voskuhl, 2012).

Sex hormones have also been shown to control neural growth factors such as BDNF, GDNF, IGF-1, and VEGF (Kipp et al., 2012) which may also contribute to their neuroprotective effects. Progesterone, an ERβ ligand, has a neuroprotective effect on oligodendrocyte differentiation (Crawford et al., 2010), and promotes myelination (Chezik and DeKeseray, 2010). Taken together, it is likely that the therapeutic effects of pregnancy on MS, are due to a combination of sex hormones since these two hormones are present at high concentrations during the third trimester.

Theiler's virus-induced demyelination as a model for MS

The etiology of MS is unknown, although epidemiological studies have implicated an infective agent as a possible initiating factor (Acheson, 1977). A number of viral agents including, measles, mumps, and parainfluenza type I, (Allen and Brankin, 1993) and human herpes virus simplex type 6 (Challoner et al., 1995) have been isolated from the brains of MS patients at post mortem. HHV6 has also been detected in the majority of non-MS brains, suggesting that there is a “normal brain flora.” Most recently, another herpes virus: Epstein–Barr virus has been detected in lymphoid follicles within MS brains (Serafini et al., 2007). An epidemiological survey reported the increased risk of developing MS was associated with infection with measles, mumps, and Epstein–Barr virus occurring at older ages in childhood (Hernan et al., 2001). In addition, exacerbations of MS are frequently preceded by viral infections (Sibley et al., 1985). It is also intriguing that the antiviral IFN-γ has been reported to have a beneficial effect on relapsing/remitting MS (IFN-γ, Multiple Sclerosis Study Group, 1993).

Viruses cause demyelination in different animal species: measles virus in rats; mouse hepatitis virus, Semliki Forest virus and Theiler’s virus in mice; visna virus in sheep; and herpes simplex in rabbits (Dal Canto and Rabinowitz, 1982). Theiler’s murine encephalomyelitis virus, a cardiovirus belonging to the family Picornaviridae, provides a unique model for the study of human MS for several reasons. First, Theiler’s virus is a naturally occurring pathogen of mice (Lipton, 1975; Theiler, 1934; Welsh et al., 1990), which causes an autoimmune-mediated demyelination of the central nervous system resulting in inflammatory lesions with similarities to human MS (Lipton, 1975; Lucchinietti, et al., 2000). Secondly, like human MS, susceptibility to TVID is associated with the MHC. For instance, mice of H-2Dkβκ genotype are able to clear the initial infection with Theiler’s virus by a process that involves CD4+ and CD8+ cells and these mice do not develop Theiler’s virus-induced demyelination (TVID). In contrast, infection of H-2Dkαβκ mice leads to a persistent viral infection of the CNS and results in demyelination (Lipton and Melvold, 1984; Rodriguez and David, 1985).

Theiler’s virus infection in mice represents not only an excellent model for the study of the pathogenesis of MS but also a model system for studying disease susceptibility factors, mechanisms of viral persistence within the CNS, mechanisms of virus-induced autoimmune disease and the role of hormones in disease modulation.

The impact of gender in Theiler’s virus infection

Studies of the effects of sex hormones in virus models of MS are limited and contradictory (Alley et al., 2003; Fuller et al., 2007; Hill et al., 1998; Sieve et al., 2004). One study demonstrated that female mice were more susceptible to early Theiler’s virus disease (Hill et al., 1998). Another study showed that male SJL/J mice had higher viral loads and lower virus-specific antibody levels during the early phase of the disease and then developed worse demyelinating disease compared to females (Alley et al., 2003). In our studies, both male and female SJL/J mice developed similar levels of CNS inflammation (Sieve et al., 2004) but further analysis has revealed more axonal loss in male mice compared to female mice suggesting a neuroprotective role for estrogen (Young et al., 2010). In Theiler’s virus infection of C57L/J mice, estrogen also appears to play a protective role since castration increased the susceptibility to TVID and prolonged treatment of castrated mice with estrogen restored the resistance to the level of control mice. Mice treated with estrogen showed a significantly decreased level of virus-specific Th1 responses, both in the periphery and in the CNS. In addition, in vitro estrogen treatment inhibited viral replication directly in macrophages, consistent with the lower level of viral RNA in microglia/macrophages in the CNS from castrated estrogen-treated mice compared with controls. Also, estrogen treatment inhibited VCAM-1 expression induced by tumor necrosis factor-alpha in cerebrovascular endothelial cells via...
inhibition of nuclear factor-kappa B (NFkB) (Fuller et al., 2007). Overall, estrogen treatment appears to exert its effects on viral replication, induction of immune responses, as well as infiltration of activated immune cells into the CNS via inhibition of NFkB function. However, the neuroprotective effects of estrogen on the late demyelinating disease have not been studied in this model.

Hormone treatment in MS patients

The Pregnancy in Multiple Sclerosis (PRIMS) European multicenter study, enrolled 254 pregnant women with MS. Data was collected on the average number of relapses that occurred during the three months before pregnancy, during pregnancy, and three months after delivery. During pregnancy, the relapse rate decreased especially in the third trimester, coinciding with the highest levels of estrogen and then relapses increased markedly upon delivery when levels of estrogens fall (Abramsky, 1994; Confavreux et al., 1998; Gold and Voskuhl, 2009; Rinta et al., 2010; Stuart and Bergstrom, 2011). Improvements in disease have also been observed when comparing pre-menopausal and post-menopausal patients noting that as endogenous estrogen levels wane in post-menopausal patients, the relapse rate increases (Smith and Studd, 1992). Clinical trials have shown that estriol may indeed be playing a role in disease modulation in MS patients (Smith and Studd, 1992). Clinical trials have shown that estriol may indeed be playing a role in disease modulation in MS patients (Smith and Studd, 1992).

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Conclusions

MS is both an immunologically-mediated and a neurodegenerative disease therefore potential therapies should be targeted at both facets of the disease.

References


