Hormones and Behavior 63 (2013) 315–321

Contents lists available at SciVerse ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Hormone and immune system interactions in demyelinating disease

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ARTICLE INFO

Available online 5 November 2012

Keywords:
Multiple sclerosis
Sex hormones
EAE
Theiler's virus
Estradiol
Estriol

ABSTRACT

This article is part of a Special Issue "Hormones & Neurotrauma".

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.

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Contents

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

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0018-506X/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.yhbeh.2012.10.014

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 (Lucchinetti 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–Schonlein purpura, IgA nephropathy, Goodpasture's syndrome and membranous nephropathy (Beeson, 1994). The most female sex-biased disease is Sjörgen'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 afflict men more commonly, the most male biased disease is thromboangiitis 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). However, in human 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 autoreactivity 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/B7-1 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

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