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Review

Multiple sclerosis: Neuroprotective alliance of estrogen–progesterone and gender

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ABSTRACT

The potential of 17β-estradiol and progesterone as neuroprotective factors is well-recognized. Persuasive data comes from *in vitro* and animal models reflecting a wide range of CNS disorders. These studies have endeavored to translate findings into human therapies. Nonetheless, few human studies show promising results. Evidence for neuroprotection was obtained in multiple sclerosis (MS) patients. This chronic inflammatory and demyelinating disease shows a female-to-male gender prevalence and disturbances in sex steroid production. In MS-related animal models, steroids ameliorate symptoms and protect from demyelination and neuronal damage. Both hormones operate in dampening central and brain-intrinsic immune responses and regulating local growth factor supply, oligodendrocyte and astrocyte function. This complex modulation of cell physiology and system stabilization requires the gamut of steroid-dependent signaling pathways. The identification of molecular and cellular targets of sex steroids and the understanding of cell–cell interactions in the pathogenesis will offer promise of novel therapy strategies.

1. Introduction

Demyelination in the central nervous system (CNS) is the pathological hallmark in multiple sclerosis (MS), which is a primary inflammatory process that leads to CNS damage and neurological deficits. Demyelination disables saltatory conduction and leads to loss of neural functions. Furthermore, demyelinated axons become more vulnerable to environmental stressors. The initial trigger(s) inducing demyelination are still unclear [127,212]. Acute lesions are believed to begin with phagocytosis of normal myelin sheaths by macrophages in the presence of infiltrating T lymphocytes. This concept is supported by studies of an animal model for MS, experimental autoimmune encephalomyelitis (EAE), where the myelin sheath is targeted by auto-reactive $CD4^+$ T cells and lymphocyte infiltration is a primary event [128]. However, there is evidence that at least in some cases of MS, oligodendrocyte stress or even death is the initial event in MS lesion formation with intact myelin sheaths [15,137,140,211]. Apoptotic oligodendrocytes and activated microglia are found in the absence of inflammation with few or no myelin phagocytes or lymphocytes in early MS lesions [15,211]. Death of oligodendrocytes and the formation of new MS lesions could be triggered by viral infection, followed by microglial activation and recruitment of virus specific $CD4^+$ and $CD8^+$ T cells and macrophages into lesions. In that regard, the oligodendrocyte-myelin unit as a target of sex steroids is of special importance.

The rationale for almost all therapies for MS has been to reduce inflammation. Immunomodulatory therapies, such as interferon-β, glatiramer acetate or mitoxantrone have considerably improved the therapeutic options for patients with MS. These agents reduce relapse rates and reduce appearance of magnetic resonance

Abbreviations: ACTH, adrenocorticotropic hormone; ADEM, acute disseminated encephalomyelitis; AF2, activation function domain 2; AHL, acute hemorrhagic leukoencephalitis; Akt, serine/threonine protein kinase; BDNF, brain-derived neurotrophic factor; CCL, chemokine ligand; CIS, clinically isolated syndrome; CNS, central nervous system; CREB, cAMP response element binding protein; E, estrogen; EAAT, extracellular amino acid transporter; EAE, experimental autoimmune encephalomyelitis; eNOS, endothelial nitric oxide synthase; ER, estrogen receptor; ERK, extracellular-regulated kinase; F, female; FGF, fibroblast growth factor; GDNF, glial-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; IGF-1, insulin-like growth factor-1; IL, interleukin; K, kinase; LH, luteinizing hormone; LPS, lipopolysaccharide; M, male; MAP, mitogen-activated protein; MNAR, modulator of nongenomic action of estrogen receptor; MS, multiple sclerosis; NFκB, nuclear factor kappa B; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NMO, neuromyelitis optica; P, progesterone; PC 12, pheochromocytoma cell line 12; PELP1, proline-, glutamic acid-, and leucine-rich protein 1; PI3-k, phosphoinositide-3 kinase; PPMS, primary progressive MS; PR, progesterone receptor; ROS, reactive oxygen species; RRMS, relapsing–remitting MS; SH3, Src homology 3 domain; Src, sarcoma; T, testosterone; TGFβ, transforming growth factor β; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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imaging (MRI) – enhancing lesions. However, their efficacy in preventing accumulation of disability and their impact on disease progression is uncertain [213]. Identifying a drug that prevents oligodendrocyte damage, stimulates endogenous myelination and spares axon degeneration would theoretically reduce the rate of disease progression [121].

The discovery of the endogenous potential of the adult brain to react to demyelinating events has open up new avenues in searching for effective approaches to acute and chronic neurodegenerative pathologies. There is a growing recognition that the physiological functions of gonadal steroid hormones estrogens (E) and progesterone (P) fluctuate dramatically during the ovarian cycle and are maintained at high levels during pregnancy. It is a well-recognized feature of MS that there is a significant decrease in the rate of relapses in the last trimester of pregnancy [46]. It seems probable that the basis of this phenomenon lies outside the CNS predominantly being the result of hormone-mediated dampening of the T cell-dependent inflammatory activity leading to fewer and less severe episodes of demyelination. Nevertheless, there is also a growing body of evidence that high steroid hormone levels dampen directly brain intrinsic inflammatory events through the modulation of astrocyte responses [198]. In this study, conditional knockouts for estrogen receptor-alpha (ERα) were studied. The major observation was that an astrocyte knockout completely prevented ERα ligand neuroprotection such as inflammation and axon loss in the experimental autoimmune encephalomyelitis (EAE) animal model, whereas a neuronal knockout had no effect. Thus, the authors conclude that ERα signaling in astrocytes is essential for cell protection. These direct effects might be at least one important component of pregnancy-associated amelioration of clinical signs of MS. The individual contributions of peripheral and central estrogen action on MS symptom amelioration remain to be sorted out in future studies.

The myelin sheath is a unique component of the nervous system that functions to maximize the efficiency and velocity of action potentials transmitted through nerve cells. Myelin is an extension of the plasma membrane of Schwann cells in the peripheral nervous system and oligodendrocytes in the CNS. The neuronal participation in signaling myelination has been examined using Schwann cell/neuronal co-cultures, and axonal contact has been found to be essential for peripheral nervous system myelination [30,40]. Contrary to the case for Schwann cells, the presence of growth factors and chemically defined media has been found to be sufficient in producing myelin-like sheets in cultured oligodendrocytes, independent of neurons [172]. One of those factors is P [3] highlighting the important role of sex steroids in myelin formation and/or maintenance.

In the present survey, we delineate the importance of E and P in MS pathology. First, we will present an overview about steroid synthesis in the brain and discuss the relevance of both steroids in brain development and neuroprotection as well as signaling-events involved. After this general part, we will focus on the relevance of E and P for protection in demyelinating disorders, such as MS. A brief clinical as well as pathological presentation of the disease will be followed by a discussion of gender differences in MS and related disorders. We further delineate hormone-mediated oligodendroglia-protection (i.e. interaction of E/P with oligodendrocytes and their progenitors) but do not discuss neuroprotective effects in MS (effects on neurones) which has been performed elsewhere [80,115]. Lastly, we will briefly highlight effects of purines on oligodendrocyte physiology and pathology. By contrasting purinergic and hormonal signaling events, we will show that E and P act in the brain as a sort of glia transmitter additionally to executing classical hormonal effects, i.e. released by a cell or a gland in one part of the body that sends out messages that affect cells in other parts of the organism.

2. The brain as source of steroid production and steroid target

Steroid hormone biosynthesis requires a set of enzymatic conversions and biochemical precursors. Textbook knowledge tells us that the primary source of E and P production are the ovaries in females and, although to a much lesser extent, the adrenal glands and, with reservations, the testes in males. After menopause, adipose tissue in females partially takes over E synthesis, thus providing slightly higher E plasma hormone values in females compared to males. It is noteworthy that before but also after the onset of menopause, a large range of individual plasma hormone levels can be observed in females covering an order of magnitude by a factor 10 or more between age- and body mass-matched persons. Thus only approximations can be made in terms of neural regulation and neuroprotection that individual susceptibilities for steroid-related affections exist within the female population of the same age structure.

The synthetic pathway of steroid synthesis involves cholesterol as a starting point and its metabolic conversion to pregnenolone. This first critical enzymatic step is regulated by hormones such as adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH). With respect to E synthesis, pregnenolone can be further converted into P or P metabolites which might then form routes for further androgen synthesis. Estrogen formation finally requires the P-450 enzyme complex aromatase which uses testosterone (T) or 4-andostenedione as precursors for 17β-estradiol or estrone production, respectively. The aromatase is another critical and highly regulated enzymatic site to control E formation (*for additional information about the exact synthetic and regulatory pathways see Geneva Foundation for Medical Education and Research*, http://gfmer.ch/Books/Reproductive_health/Steroid_hormone_metabolism.html).

It has been demonstrated more than 40 years ago in various animals including rodents and birds that the brain itself is an additional important source for local estrogens [33] and represents a target for steroid hormones involving steroid receptors which, at that time, had not yet been detected [146]. However, already another 25 years before that, first effects of E on neurotransmitter systems in the CNS have been reported [146]. Today, we know that *de novo* E and P production occurs in both sexes in many brain regions, in different cell types, and under a wide spectrum of physiological and pathophysiological conditions [78]. The widespread occurrence of all types of classical nuclear ER and progesterone receptors (PR) in mammalian brain tissue throughout the whole lifespan clearly underpins the importance of both steroid hormones for perpetuation of proper CNS function [27,178].

Since both steroid hormones have been shown to influence inflammatory responses, anxiety and cognitive functions, it should be accentuated that a malfunction of local brain steroid formation might comparably be implicated in the etiology of neurological and neurodegenerative processes as it is described for circulating steroids. For example, increasing evidence indicates that hippocampus-derived estradiol plays a role in synaptic plasticity and neuroprotection, rather than estradiol originating from the gonads [59]. In the following, we will highlight several basic aspects of brain E synthesis, E-mediated neuroprotection and the underlying cellular signal transduction pathways before we focus in the further sections on the complex relationship between E/P and MS.

2.1. A grasp from the past – learning from brain development

The developmental role of E for processes of brain maturation and neuronal differentiation has convincingly been depicted in a large number of cell culture and animal studies over the past decades. Although to a lesser extent, P also appears to contribute to