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Sex Hormones and Gender Differences in Multiple Sclerosis: A Review

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Abstract

Multiple sclerosis (MS) is an autoimmune neurological disorder characterized by injuries to the central nervous system (CNS) neurons made by a dysregulated immune system. It is well known that the prevalence and pathophysiology of MS differs between men and women. Therefore, sex hormones have drawn the attention of researchers as a potential factors playing role in the disease pathophysiology. In the present study, we aimed to review recent findings on the role of the three main sex hormones (i.e. estrogen, progesterone, and testosterone) and their derivatives in the MS pathophysiology and their potential as a possible treatment for this disorder. We found that there are numerous evidence that these hormones play fundamental role in MS through various mechanisms related to the both nervous and immune system. Additionally, these hormones should be considered as potential treatments for MS which may help slow the disease course down, relieve the symptoms and improve its prognosis.

Keywords

Multiple Sclerosis, Sex Hormones, Estrogen, Progesterone, Testosterone

Abbreviations

MS: Multiple sclerosis,

OL: Oligodendrocyte,

PPMS: Primary progressive multiple sclerosis,

EAE: Experimental autoimmune encephalitis,

ER-β: Estrogen receptor-β,

TH-1: T helper-1,

DTI: Diffusion tensor imaging,

OPC: Oligodendrocyte progenitor cell,

TLR: Toll-like receptor,

DHP: Dihydroprogesterone,

THP: Tetrahydroprogesterone,

IGF: Insulin- like growth factor,

MBP: Myelin basic protein,

DHT: Dihydrotestosterone,

BDNF: Brain-derived neurotrophic factor

Introduction

Multiple Sclerosis (MS) is a common neurological disease causing physical and mental disabilities in the affected individuals. In 2013, 2.65 out of 10,000 people suffered from the disease and an average of 2.5 million people are also added to the number of MS sufferers annually (Belbasis et al.; Rotstein et al.).

MS symptoms may range from mild to very severe symptoms, including motor disorders (e.g. spasticity and paresis), sensory and vision impairment, fatigue, sexual, bowel, and bladder dysfunction, depression, and cognitive problems (Rommer et al.). The disease's etiology is not completely recognized, however, it is speculated that the MS incidence is mediated by interaction of various immunologic, genetic, hormonal, and environmental factors (Angeloni et al.).

MS pathology is basically related to the dysregulated function of the immune system. Infiltration of T lymphocytes, natural killer cells, and macrophages are responsible for this dysregulation, leading to tissue injury and inflammation, axonal damage, death of oligodendrocytes (OLs), and demyelination. However, activated microglia are the main cells causing inflammation and tissue damage in the late stages of the disease (Dendrou, Fugger and Friese; Maglione et al.; Loma and Heyman). These immunologic auto-reactions form a complex of injured and demyelinated axons, inflammatory cells, and astrogliosis which all together form CNS plaques characteristic of MS in MRI scans of the brain and spinal cord (Ghasemi, Razavi and Nikzad).

There are several evidence that the pattern and severity of symptoms and also prevalence of MS differ between men and women. The incidence of MS is lower in men than in women and, on the other hand, women are usually diagnosed at an earlier age than men and will have more benign disease course. It is established that MS causes more severe clinical and psychological disabilities in men (Lopez-Alava

et al.). Also, the prevalence of primary progressive MS (PPMS), which predicts poorer prognosis, is lower in women than in men (Kipp et al.). Therefore, the progress of MS in men is usually faster, accompanied with more severe symptoms and poorer performance in cognitive tests compared to women, and will lead to more disabilities. Such differences between the sexes are attributed to genetic background (sex chromosomes, in particular) and sex hormones (Klein and Flanagan). There are several evidence that the sex hormones play substantial role in regulating the MS disease pathophysiology and severity of symptoms, which will be reviewed and discussed further on.

In the present review study, we specifically focused on the effect of sex hormones on different aspects of MS disease. We reviewed more recent investigations published in authentic journals to obtain a coherent understanding of new findings regarding the role of the main sex hormones (i.e. estrogen, progesterone, and testosterone) in MS pathophysiology, and promising results shedding light on possible treatments for MS.

Sex hormones:

Estrogen

Estrogen has been becoming increasingly attractive as a potential agent for reducing MS relapses and slowing the disease course. In 1998, Confavreux et al. claimed that the rate of relapses in female MS patients was significantly decreased over the third trimester of pregnancy, which is characterized by increased serum level of estrogen (Confavreux et al.). This finding was highly suggestive of a potential role for estrogen in alleviating MS course and the disease symptoms. One year later, in an animal study, Kim et al. administrated mice model of experimental autoimmune encephalomyelitis (EAE) with estriol, a subtype of estrogen mainly targeting estrogen receptor-β (ER-β), to increase the serum level of estriol to its level during pregnancy. Similarly, they found that high serum level of estriol is associated with milder EAE course (EAE is an animal model of MS mediated by T helper-1 (Th-1) cells and administration of estriol induced production of IL-10, which downregulates the activity of Th-1 cells) (S. Kim et al.). There are also findings of behavioral studies in animal models indicating a potential role for exogenous estrogen in improving the cognitive function of MS models. Alihemmati et al, for instance, in an animal study on rat model of MS found that intra-hippocampal injection of estrogen is significantly correlated with improved spatial memory in the Morris water maze task (ZARRIN, HATAMI and ALIHEMMATI).

Estrogen is believed to intervene in MS disease pathophysiology through various mechanisms, by directly acting on the CNS or indirectly acting on the immune system function. In the following, we will go into more details to discuss these mechanisms.

Estrogen applies its effects by acting on two receptors: ERα and ERβ. Both these receptors may be considered as potential targets in estrogen therapy studies. In 2016, Voskuh et al. investigated the effect of ERβ stimulation by its ligands in treatment of EAE. Their results showed that clinical EAE severity score was reduced in mice treated with ERβ ligand, and this effect was applied across different genetic backgrounds and in both genders. Therefore, they tried to investigate the possible mechanisms through which ERβ stimulation alleviates EAE. They found that ERβ ligand has protective effect against axonal damage and demyelination in spinal cord of EAE models, preserves neurons and synapses in the cerebral cortex, and restores the damaged axons and their myelin sheath. Additionally, using MRI scans, they found that ERβ ligand treatment reduced cortical atrophy in the EAE mice. ERβ ligand also declines the activated microglia in the CNS, explaining its anti-inflammatory properties (Itoh et al.). Another animal investigation using diffusion tensor imaging (DTI) showed that ERβ ligand can induce remyelination in the mouse model of MS, which was in accordance with immunohistochemical findings of the brain tissue biopsies (Atkinson et al.). In 2018, Kim in another in-vivo investigation on the EAE model revealed that treatment with ER-β ligand increases the oligodendrocyte progenitor cells (OPCs) and maturation of OLs, and decreases the production of pro-inflammatory cytokines. She also found that treatment with ER-β ligand might induce remyelination by activating the cholesterol synthesis pathway genes (Kim).

Cellular and molecular investigations suggest a potential role for estrogen in proliferation of neuroprotective cells. Both OLs and OPCs are found to express membrane ERα and ERβ. Binding of ligands to ERα and ERβ activates these receptors on OLs and OPCs leading to proliferation of OPCs, differentiation of OLs, and their survival after demyelination following autoimmune reactions (Struble et al.; S. Kim et al.).

Estradiol is produced by not only ovaries, but also by neurons of the brain. Through autocrine and/or paracrine processes, estradiol produced by neurons acts on their ERs and increases their survival. It is believed that the process of neurodegeneration, as occurs in MS, leads to elevated production of estradiol by neurons (Arevalo, Azcoitia and Garcia-Segura). Microglia only express ERβ, but not ERα. It is claimed that the activity of microglia is suppressed by stimulation of its ERβ (Paterni et al.).

Another aspect of neuroprotective properties of estrogen is preserving neurons from stress and apoptosis. It is previously demonstrated that oxidative stress in the brain tissue is significantly higher

in patients suffering from MS than in healthy population. Additionally, oxidative stress is associated with neuronal damage and may contribute to worse disease outcome (Choi et al.; Padureanu et al.; Katarina et al.). In an animal study on rat model of MS, it was observed that estradiol prevents the oxidative stress by removing free radicals and reactive oxygen species (Hatami and Khajehnasiri). This findings suggest anti-oxidant role for estradiol in the MS, which may alleviate the tissue injury and the disease progression. Estrogen therapy also reduces glutamate-induced apoptosis and preserves the normal electrophysiological function in neurons (Sribnick et al.).

Another protective mechanism of estrogen against MS is regulation of immune system function. However, especially in lower doses, estrogen reinforces the immune functions through various mechanisms, there is evidence that high doses of estrogen decrease the expression of pro-inflammatory cytokines (e.g. TNF, IL-1, IL-6, IL-17) and increases the activity of regulatory T-cells and production of IL-10 (Bouman, Heineman and Faas; Klein and Flanagan; Nekrasova and Shirshev). IL-10 regulates the activity of Th-1 cells, which are known to stand for the autoimmune cellular responses in MS disease (Rutz et al.).

In EAE models, also, estrogen is shown to have anti-inflammatory properties. Estrogen modulates the immune function by inducing CD4+ and CD25+ regulatory T cells. Additionally, ER agonists can cause the death of immune cells by stimulating the Fas-Fas ligand pathway of apoptosis, leading to immunosuppression (Klein and Flanagan). Estrogen reduces the Th-17 cells and their production of IL-17 and increases the number of regulatory T cells (Klein and Flanagan; Garnier et al.). Stimulation of ERα suppresses the activity of follicular helper T cells and the autoimmune processes. Follicular Th (a subset of CD4+ T cells) is another immune cell which is showed to take part in the inflammatory processes of MS pathogenesis, leading to formation of plaques and lesions in the CNS (D.-H. Kim et al.; Schmitt).

Another mechanism by which estrogen suppresses immunity-induced inflammation in the CNS is reducing the expression of MMP-9. MMP-9 allows T lymphocytes to pass the blood brain barrier and enter the CNS, leading to inflammation and tissue injury. Declined expression of MMP-9, therefore, may decrease the inflammation and subsequent tissue injury in the CNS (Spence and Voskuhl).

Besides animal and in-vitro studies, there are evidence of clinical investigations revealing the beneficial effect of estrogen in the treatment of MS. In a clinical trial study, 10 non-pregnant women aged 28 to 50 were treated with oral estriol (8 mg/day). Monthly MRI scans of these patients revealed that long-term treatment with estriol was significantly correlated with decreased number of enhanced lesions, and when the treatment was stopped, these lesions increased to the pre-treatment levels.

Interestingly, when the treatment was pursued, the number of lesions deceased again. These findings strongly support the protective role of estriol against MS lesions in the human subjects (Sicotte, Liva, et al.). The findings of another clinical investigation using MRI exhibited that treatment with estriol spared certain regions of the gray matter in MS patients, providing another evidence on the neuroprotective effects of estrogen subtypes (MacKenzie-Graham et al.).

Progesterone

Similar to estrogen, progesterone also affects the MS pathophysiology and course through various mechanisms. In-vitro findings suggest anti-inflammatory role for progesterone by decreasing the expression of pro-inflammatory cytokines TNFα and IL-1β, and suppression of microglia activity (JIANG, WANG and LI). This hormone increases the ratio of Th2 anti-inflammatory cytokines to Th1 pro-inflammatory cytokines, which suppresses the inflammatory responses (El-Etr et al.; Alejandro Federico De Nicola et al.). Progesterone contributes to regulating the immune system by decreasing the number of Th17 cells and increasing the level of FOXP3 regulatory T cells. This steroid also deactivates the pathway of NF-Kappaβ and Toll-like Receptors (TLRs), thereby modulating the immune system activity.

In studies on EAE animal models, progesterone therapy has been shown to increase the level of 5α-reductase mRNA and aromatase mRNA compared to other non-treated EAE models. Aromatase contributes to the synthesis of estrogen and 5α-reductase contributes to the synthesis of progesterone derivative, dihydroprogesterone (DHP) (Laura Garay, Paula Gonzalez Giqueaux, et al.). DHP, produced by OLs as a result of changes in progesterone, is involved in protecting the myelin sheath (Schumacher et al.). Progesterone, 3α,5α-tetrahydroprogesterone (THP), and 5α-DHP influence the transcription of factors such as SOX-10, EGR-1, EGR-2, EGR-3, FOSβ, thereby affecting the myelination process in the CNS. Progesterone, THP, and DHP also increase the myelin basic protein (MBP) and IGF-1 in OLs (Christianson, Mensah and Shen; Laura Garay, Maria Claudia Gonzalez Deniselle, et al.),

Another aspect is decreasing oxidative stress and regulating the level of proteins effective in the process of apoptosis, leading to prolonged neuronal life (Melcangi, Giatti and Garcia-Segura), dendritic growth, and neurogenesis (Kipp et al.). It is also established that progesterone supresses tissue inflammation and apoptosis in the brain, following brain damages (Stein, Wright and Kellermann). In an animal study on EAE mice model, De Nicola et al. administrated a group of mice with progesterone one week before induction of EAE, while the control group did not receive progesterone. They found

that mice received progesterone had better disease outcome and less severity. Furthermore, the inflammatory processes were milder in mice receiving progesterone and they had reduced demyelination (Laura Garay, Maria Claudia Gonzalez Deniselle, et al.). It is discussed that increased production of neurosteroids, including progesterone, in the brain will confer anti-inflammatory and neuroprotective effects through autocrine and paracrine processes (ALEJANDRO F De Nicola et al.).

Testosterone

Testosterone and its active metabolite, dihydrotestosterone (DHT) have a higher serum level in men, similar to other androgens (Klein and Flanagan). As men grow older, their testosterone level decreases. It is proposed that low serum testosterone contributes to increased incidence of MS in men in older ages, and is associated with worse disease prognosis (Triantafyllou et al.; R Bove et al.). However, the contribution of androgens to MS prevalence is not limited to men. A clinical investigation on female patients with MS also found that these patients have significantly lower serum level of testosterone than healthy female individuals (Nikseresht, Lima and Dorche). An old clinical trial study on 10 men suffering from RRMS revealed that administration of testosterone in the form of gel was significantly associated with improved cognitive function and slowed brain atrophy, however, number or volume of the lesions did not change significantly (Sicotte, Giesser, et al.). On the other hand, it has been observed that brain atrophy in MS may be associated with lower levels of testosterone (Riley Bove et al.). These findings warrant further clinical studies on the role of testosterone in MS symptoms and brain changes.

Several studies have been dedicated to investigating the underlying mechanisms of the role of testosterone in MS disease. Testosterone and its metabolites have a proven role in protecting neurons, decreasing neural death and enhancing the function of the nervous system (L. Garay et al.). These hormones modulate the growth and division of nerve cells and play an important role in nerve tissue repair. Additionally, neuroprotective effects of testosterone may be due to increased activity of OLs or inhibition of microglia and astrocyte activity. This hormone can also enhance the remyelination process (Tang et al.; Laura Garay, Paula Gonzalez Giqueaux, et al.).

There is evidence that castration of male mice is associated with more severity of EAE, which is suggestive of a potential role for androgens in the pathophysiology of EAE. Administration of exogenous testosterone in these models is associated with relief of symptoms and reduced expression of inflammatory cytokines TNFα and INFγ, induced an immune shift from Th1 to Th2 cells, and increased the expression of Th-2 anti-inflammatory cytokine IL-10 (Collongues et al.). In addition, by

inhibiting the pathway of NF-kappa B, testosterone reduces the amount of IL-6 production and thus suppresses inflammatory processes (Oertelt-Prigione). Accordingly, testosterone has an immunomodulatory and anti-inflammatory potential. In addition, testosterone promotes the remyelination, increases the synthesis of brain-derived neurotrophic factor (BDNF), and protects the neurons from oxidative stress and glutamate-induced toxicity, as does estrogen (Collongues et al.).

Discussion and conclusion:

MS physical and psychological symptoms may make the patients partially or completely disabled, leading to decreased patients' productivity and quality of life, and impose a heavy burden on health care system resources (Jones et al.). It is noteworthy that providing care to the patients with more severe symptoms will be more costly (Kobelt et al.).

Multiple factors are found to contribute to the risk of developing MS and also its clinical prognosis. Sex hormones, including estrogen, progesterone, testosterone, and their derivatives are one of the most considerable factors. These hormones are found to have both neuroprotective and immunomodulatory properties, through which play fundamental role in the disease pathophysiology and symptoms. As discussed earlier, there are evidence that sex hormones play role in reinforcing the remyelination process, shifting the production of cytokines from pro-inflammatory to anti-inflammatory, and protecting the neurons from oxidative stress and apoptosis.

However, as mentioned above, there are clinical trial studies on the effectiveness of administration of exogenous sex hormones (e.g. testosterone), yet more clinical investigations are warranted to increase our knowledge about the effectiveness of these treatments in long-term periods, their safety and potential side effects. Furthermore, it is still remaining unclear whether administration of exogenous sex hormones, such as estrogen, can reverse the disease progression and symptoms and also make the CNS lesions disappear.

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