REVIEW

Effect study of sex hormone in the multiple sclerosis of common neurological disorders

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Abstract: Multiple sclerosis (MS) is one of most common neurological disorders, mainly affecting women. The central nervous system (CNS) of this autoimmune disease is characterized by intermittent or chronic damage to the myelin sheaths (demyelination), local inflammation and axonal degeneration. During the early relapsing/remitting stages of MS, myelin can regenerate. However, as the disease progresses, both amount and activity of regenerated axons becomes insufficient, leading to impaired axon conduction, neurodegeneration and the worsening symptoms. Epidemiological study found that distinct symptom alleviation of diseases at a certain periods would be shown in women during pregnancy. The following basic researches indicated that sex hormones especially progesterone can significantly reduce the disease severity, moreover, the protective effect of sex hormone on the nervous system has become the research focus.

Keywords: Sex hormone; multiple sclerosis; progesterone; estrogen.

INTRODUCTION

Multiple sclerosis (MS) is one of the common neurological disorders, with the main pathological characteristics of repeated demyelination, focal inflammation, axonal degeneration. At present, the therapeutic drugs are mainly limited in immune regulation and anti-inflammation. However, these can only relieve the symptoms rather than alleviate the disease progress. There are more females than males with the disease, 20 to 40 years as the peak age of onset. Among those, most female patients are in childbearing age, and 10% patients are with first onset during pregnancy (Confavreux and Vukusic, 2006). As to females with MS, changes in sex hormone have a great influence on the MS process and disease severity (Gold and Voskuhl, 2009).

Clinical study in sex hormone and MS

R ecent studies has considered that MS is an immune disease regulated by T helper (Th1). For immune system, the balance of Th1/Th2 plays an important role in the progression of the disease. Through the alteration in tilt direction, such as expressing Th1 and enhancing Th2 reaction level, it is able to realize the transformation of the disease. The current immunotherapy drugs, interferon 1ß, interferon 1 and glatiramer, achieve the therapeutic effect in the relapsing - remitting MS through the above mentioned pathway. In pregnancy, studies have found the immune deviation, that is, there are suppression in Th1 and enhancement in Th2 function (Leitner, 2010 and Stuve *et al.,* 2010). In the clinical study of sex hormone in the treatment of MS performed by Sicotte *et al* (2007), oral estriol in 6 months was administrated on 10 patients (6 cases with relapsing-remitting MS and 4 cases with secondary progressive MS). On relapsing-remitting patients, experiments were prolonged with 4-month treatment period and the progesterone was combined during the prolonged period in case of the proliferation of endometrium. With the assistance of magnetic resonance imaging, it found that significant alleviation was shown in the injury area of MS and the peripheral immune cell cytokines was also reduced. When quitting the estriol treatment, the injury was returned in the level before treatment, while the injury was improved after continuing the previous treatment. To discuss the prevention of progesterone and sex hormone in MS relapse after childbirth, researchers started a double-blind and placebo - controlled trial: the study of progesterone in postpartum (Vukusic *et al.,* 2009). So far, 171 pregnant MS patients have taken Nomegestrone Acetate randomly. 300 female cases have been enrolled temporarily, still no find in the long-term adverse effect (Vukusic *et al.,* 2009).

Certain preliminary studies have suggested that testosterone may has effectiveness on male MS. To discuss the effect of testosterone on MS, perspective study performed by some researchers has found that small dose testosterone can significantly improve both

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symptoms and basic severity of MS (Sicotte *et al.,* 2007). Currently, the relatively consistent view on the relationship between pregnancy and MS is that at the early pregnancy, the symptoms will be obviously improved, while after pregnancy, the symptoms will be continuously deteriorated to the level before pregnancy (Schumacher *et al.,* 2008).

Basic research on sex hormone and MS

Animal model

Experiment allergic encephalomyelitis is a delayed allergic autoimmune disease, guided by homogeneous, homogeneous heterogeneous type and heterogeneous heterogeneous type-induced encephalitis antigen, generated from experimental sensitive animals, mediated by cellular immune response and characterized by white matter demyelination of central nervous system. Due to the similarity between the symptoms induced by this model and MS clinical performance, this model is always regarded as the standard model for researching MS, which also has solved the problems of animal model in the MS research (Baker *et al.,* 2011 and Batoulis *et al.,* 2010).

Estrogen

*I*n the animal model, it has been found that no matter whether it is at pregnancy, even the small dose estrogen can postpone the disease activity or suppress the disease progress. Estrogen has the ability to reduce the penetration of inflammatory factors and pro-inflammatory factors, such as the generation of tumor necrosis factor α, interleukin (IL) 4, IL-5 and IL-10. Those pro-inflammatory factors are mostly from activated spleen and mononuclear cell of central nerve. Research has found that the suppression effect produced by minimum effective dose has a different results in different mice groups, suggesting that due to the individual difference, the sensitivity of estrogen receptor difference is different, having a great influence on the disease severity (Garidous *et al.,* 2004 and Giraud *et al.,* 2010).

Estrogen has two receptors, estrogen receptor α (ER-α) and ER-β, playing key protective role. Researches have showed that lymphocyte express estrogen receptors, and the effect of lymphocyte is also simulated and regulated by sex hormone. The pleiotropic actions of estrogen, mainly through ER gene mediated by ER and cell membrane, play the regulation of antigen - presenting cells, endothelial cells and even the different brain cells, and down - regulate inflammatory response and direct neuroprotection (Manthey and Behl, 2006).

Progesterone

In cerebral ischemia and cerebral trauma animal model and clinical experiments, progesterone has the effects in promoting myelin sheath and protecting nerve for central nervous system (Wang *et al.,* 2010). Progesterone is able to protect the survival of neuron after trauma, withstand the toxic effect of glutamic acid on neuron, and promote the functional recovery of injured neurons *et al*. In the experiment of motor neuron degeneration and necrosis for Wobber mice group, it has been indicated that progesterone can not only alleviate disease course, protect neural apoptosis and enhance axonal transport, but also promote the growth of nerve growth factor and reduce the oxidative stress response (Stein, 2008 and Gibson *et al.,* 2008). Progesterone also presents a great positive role in neural myelin sheath outside neurons. As to oligodendroglia cells in central neural system, after using progesterone, myelin basic protein expression is increased, showing myelin synthesis is significantly improved compared that with no using progesterone (Chesik and De Keyser, 2010 and Patrikios *et al.,* 2010). Moreover, progesterone also can promote the toxicity-mediated injury or the synthesis and differentiation of myelin progenitor cells of apoptosis nerve. Apart from the above neuron and myelin synthesis effects, progesterone also has a regulation effect in the inflammatory immune response of central nerve system, reserving Th1/Th2 balance and alleviating inflammation degree. In the experiment allergic encephalomyelitis, the inflammatory chemokine models, such as growth factor 2 and IL-1, is found transference.

Male hormone

*M*ale hormone plays correlative roles, realized mainly in ER pathway. Firstly, male hormone can be transferred into estradiol with the effect of aromatase which is expressed in the cerebral cells, adipose cells and plasma white blood cells. Secondly, the metabolic products of male hormone can directly active ER, but is distinguishing from the aromatase pathway, coming from the regulation effect of male hormone receptor. Recent researches have showed that the male hormone metabolites, like 5 α- male hormone-3 β and dihydrotestosterone, have a potential ER activity effect (Sicotte *et al.,* 2007).

Studies have found that estrogen and progesterone can improve disease symptoms through regulating autoimmunity and inflammatory response. In immune system, most molecular cells are able to express estrogen receptors. Estrogen has the effects not only in anti - inflammation, but also in pro - inflammation. In experiment allergic encephalomyelitis, estrogen used before immune can prolong the start of the symptoms and reduce disease activity. These effects are related to the decrease of T cells, penetration of macrophages and reduce of inflammatory factors' generation. Recent studies have investigated that with the effect of the estrogen receptors on cell membranes, estrogen has a little effect in the established experiment allergic encephalomyelitis (Gibson *et al.,* 2008).

The main protective mechanism of sex hormone on MS

Pro - myelin regeneration

S ome pathological studies have indicated that there exist numerous oligodendroglia neural progenitor cells undifferentiated into oligodendroglia cells in the tissues of MS patients. Moreover, oligodendroglia cells are recently considered as the key to form the myelin membrane. Oligodendroglial transcription factor (Olig 1) myelinogenesis is a crucial regulatory factor, regulating oligodendrocyte precursor cells differentiating into oligodendroglia cell and finally forming myelin sheath. However, Olig 1, generally existing in cytoplasm, plays corresponding effects only getting into cell nucleus after activation. Furthermore, the mechanism of Olig1 transported into cell nucleus is still uncertain. There are some studies manifesting that the transport process of Olig1 may be suppressed by Tat interactive protein (TIP30), because the TIP30 content in MS patients is significantly augmented, an important factor of remyelination failure. Progesterone and estrogen can promote remyelination, that is, promoting Olig1 into cell nucleus from cytoplasm. Its main mechanism is that the mutual effect between estrogen and TIP30 regulates the transcription of downstream gene, thus playing pro-myelin regeneration, based on the reason that progesterone also has the similar regulatory effect towards gene transcription (Yu *et al.,* 2010).

Anti – inflammation

The studies focused in the profile after disease starting have indicated that progesterone, through inflammatory factors, can alleviated the disease severity of MS patients, mainly showing the reduce in secretion of pro-inflammatory factors (such as IL-17 and IL-2) and the augment in secretion of anti - inflammatory factors (such as IL-10). The present studies have found that the immune regulation of lymphocyte shows a great application value in the therapeutic effect of progesterone (Labombarda *et al.,* 2010). In cluster of differentiation 19 (CD_{19}) deficiency mice, it is shown that the augment of tumor necrosis factor α and the reduce of IL-10 enable the increase of disease severity. In progesterone treatment group, it is presented that the lymphocyte is significantly increased, possibly due to the increase of IL-10; I -10 is also manifested distinctly increase in T cells or CD_8^+ single treatment group. IL-10, through suppressing antigen presentation, can prevent the generation of IL-12 and the secretion of Th1; CD_8^+, through inducing the production of interferon γ and nitric oxide, plays regulation effect and alleviates disease severity. Recently, there is no definite MS patients accompanying with chronic inflammation, while together with demyelination and axonal injury. The inflammation is considered mediation with CD_4^+ of Th1 lymphocyte as CD_4^+ can secret pro- inflammation factor interferon γ, IL-2, and tumor necrosis factor α *et al*. Meanwhile, it is also found that the Th2 factors, secreting IL-4, IL-5, IL-10 and IL-13, is significantly down regulating. Therefore, it is deducted that the auto- inflammation of MS disease is related to the balance of Th1/Th2, while progesterone has the opportunity to induce balance develop into anti-inflammatory direction.

Promoting axon regeneration

MS-induced demyelination has already occurred during relapsing remitting. Moreover, the range of axonal injury is wide, from spinal cord to cerebral cortex. Among existed animal models, it is indicated that demyelination is usually started in the 2nd - 3rd week after onset. Remyelination can be repaired by mature oligodendroglia cells, but necessarily depending on that the precursor cells of endogenic oligodendroglia cells are proliferated, differentiated and matured into myelin - producing cells. 16 mg/(kg·d) dosage was administrated by Labombarda *et al* (Labombarda *et al.,* 2010) on mice with transverse spinal cord T_{10} with progesterone in 3 days and 21 days. The results showed that the precursor cells' amount of $NG2^+/Ox42^-$ endogenic oligodendroglia cells in anterior cord, side cord and posterior cord of mice spinal white matter in the treatment group with 3 days was significantly increased than those in the control group, the mRNA of transcription factor Olig2 and Nkx 2.2 which promote the differentiation and maturity of the precursor cells of endogenic oligodendroglia cells was rising, and the expression of myelin basic protein mRNA and protein level was increased; In the treatment group with 21 days, the CCL^+ cell amount of mice spinal cord was increased, and the ratio of $CCL^+/BrdU^+$ accounting for CCL^+ cells was nearly 50%, much larger than that in control group and blank group, suggesting that progesterone had the ability to promote the precursor cells of proliferated oligodendroglia cells differentiate into mature oligodendroglia cells. Furthermore, progesterone can enhance transcription factor Olig1 mRNA and protein levels, be conducive to myelin repair, and augment the expression of proteolipid protein which is relative to the survival, metastasis and intracellular transport *et al* (Garay *et al.,* 2009).

CONCLUSION

The protective effect of sex hormone on neuron has been confirmed in traumatic brain injury animal models and in clinic. At the same time, sex hormone has the effects in significantly anti - inflammation, promoting the myelin regeneration, protecting axon injury and neuron *et al*. It is the similarity between above mentioned effects and MS clinical characteristics that pays researchers' attention. The current researches has showed that sex hormone, especially progesterone, has a significant positive effect to MS, postponing or alleviating disease severity as well as enhancing patients' life and survival quality. However, the existed researches are still limited, unavailable to explain carefully the protective mechanism of sex

hormone on MS. The basics and clinical researches on this aspect is still worth continuous efforts for scientific research crews.

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