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Review

Hormonal influences in multiple sclerosis: New therapeutic benefits for steroids

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ABSTRACT

Multiple sclerosis (MS) is one of the most common neurological disorders. It affects mainly women. This autoimmune disease of the central nervous system (CNS) is characterized by intermittent or chronic damage to the myelin sheaths (demyelination), focal inflammation and axonal degeneration. During the early relapsing/remitting stages of MS, myelin can regenerate, but as the disease progresses the remyelination of axons becomes insufficient, leading to impaired axon conduction, neurodegeneration and the worsening of symptoms. The present pharmacological treatment of MS is limited to the administration of immunomodulatory and anti-inflammatory drugs, which are only palliative and do not significantly slow progress of the disease. What are needed are agents that target different cell types in the CNS to protect axonal networks and stimulate the endogenous capacity of myelin repair. Estrogens and progestins may be the basis for such a new therapeutic approach. Although clinical observations provide only indirect or insufficient evidence for an influence of sex steroids on the progress of MS, experimental studies have shown that estrogens and progestins exert multiple beneficial effects in experimental autoimmune encephalomyelitis (EAE), a widely used MS disease model. Moreover, both types of hormones have been shown to promote the viability of neurons and the formation of myelin. These promising experimental results should encourage the launch of prospective clinical studies to clarify the influence of hormones on the course of MS and the effect of hormone treatments, in particular those presently used in contraception and hormone replacement therapy (HRT).

Contents

1. Introduction

According to a recent cross-sectional study conducted in France, the incidence of multiple sclerosis (MS) is 7.5 per 100,000 per year, but the women–men ratio is 2.6 [1]; the same study reported that requests to register as an MS patient (principally in order to receive

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free medication under the French system) were most numerous for the age groups 30–39 and 40–49 years. Intriguingly, the number of women with MS, but not of men with the condition, has increased over the last two or more decades, but the cause of this increasing gap between the sexes is unknown [2,3].

The hallmark of MS is damage to myelin sheaths. When axons lose their myelin insulation, the conduction of nerve impulses slows or even stops. The resulting clinical symptoms are very heterogeneous, as the location and severity of demyelination differ between patients [4]. In 80% of cases, MS starts with a relapsing/remitting course, which after several years may become a progressive one. This is because myelin can be extensively repaired as part of a natural healing process during the early stages, but remyelination later becomes slow and inconsistent. The pathophysiological mechanisms involved in the evolution towards a progressive disease remain poorly understood, but the irreversible degeneration of axons and a reduced capacity of the ageing central nervous system (CNS) to form new myelin sheaths are likely to be involved. There is also evidence that the efficiency of remyelination markedly differs among patients [5]. Thus, stimulating the endogenous capacity of myelin repair is an important therapeutic aim [6].

Although there is no cure for MS, several drugs, in particular immunomodulatory agents, have proved beneficial during the relapsing/remitting phase; nonetheless, the net clinical gain is modest [7]. Treatment with corticosteroids, principally high-dose intravenous or oral methylprednisolone, speeds up recovery from relapses [8]. Unfortunately, corticosteroid treatment is often referred to as "steroid treatment", which is inappropriate and creates confusion, as the generic term "steroid" refers to any molecule with a sterol skeleton, including the sex steroid hormones and synthetic steroid compounds used in contraception or hormone replacement therapy (HRT).

The physiopathological mechanisms involved in the evolution towards a progressive stage remain poorly understood, but axonal degeneration and a reduced capacity of remyelination by the aging CNS may be among the causal agents. There is thus an urgent need for new therapeutic strategies, not only targeting immune cells, but also neurons and glial cells. Estrogens and progestins may hold great promise, because of their immunomodulatory, neuroprotective and promyelination actions [9].

2. Influences of sex steroids on multiple sclerosis: clinical observations

Studies have examined the relationship between the course of MS and sex and variations in hormonal status, as well as the effects of hormone treatments (estrogens and progestagens). For instance, women reach disability milestones at older ages than men, and male sex is associated with more rapid progression and a worse outcome [10]. Differences in circulating sex hormones could also play a role in the development of MS, as suggested by the consistent observation that more women than men suffer from MS.

Changes in MS symptoms related to the menstrual cycle, with a worsening preceding menstruation, have been reported in about 40% of women with relapsing/remitting MS [11,12]. Also, two studies that used magnetic resonance imaging (MRI) to monitor MS activity across the menstrual cycle reported an association with hormone levels [13,14], although both studies were conducted over 10 years ago, when the specificity and accuracy of MRI were less good than they are now in the analysis of MS lesions. A recent study found no significant differences in MS symptom scores between the different phases of the menstrual cycle, but in a relatively small patient sample [15].

There are indications of an influence of oral contraceptives on the course of MS, but these studies are mainly based on self-reported clinical symptoms, and no prospective data exist. Two studies pointed to an improvement of MS symptoms in women taking oral contraceptives [11,15]. Concerning the risk of developing MS, two prospective cohort studies conducted among British women failed to find an association with oral contraceptive use [16,17]. The Nurses Health Study, which is among the largest and longest-running investigations of factors that influence women's health, also found no link between the use of oral contraceptives and the risk of developing MS [18].

Pregnancy has been reported to have a marked influence on the course of MS [19]. The prospective European Pregnancy in Multiple Sclerosis (PRIMS) study of 227 pregnancies found that the rate of relapse was significantly reduced during the last 3 months of pregnancy, when circulating levels of estrogens and progesterone are highest, while the relapse rate increased during the first 3 months post-partum, after the drop in sex steroid levels [20]. There is no clear evidence for an effect of pregnancy on the risk of developing MS [18].

Surprisingly little information is available concerning possible influences of menopause and HRT on the progress of MS. In a recent Swedish study, 146 women with MS were questioned about their symptoms. A worsening of MS symptoms at the time of the menopause was reported by 40%, whereas 56% reported no change and 5% a decrease in symptoms [12]. In the same study, a few women reported changes in MS symptoms in relation to the use of HRT. In a study involving 19 postmenopausal women, 54% reported a worsening of symptoms with the menopause, and 75% of those who had tried HRT reported an improvement [21].

These clinical studies do not allow firm conclusions to be drawn concerning any effect of sex steroid hormones or steroid treatments on the course of MS, because of the generally small patient samples, coupled with the use of retrospective enquiry and self-reports. Moreover, concerning the effects of contraceptives and HRT, the hormone formulations used are not always specified. Observations of changes in the symptoms of MS during pregnancy and sex differences provide only indirect evidence of a hormonal influence.

3. Experimental models in multiple sclerosis research

In spite of the lack of conclusive clinical data, strong evidence for a key role of estrogens and progestins in the pathogenesis of MS has been provided by experimental studies. An important experimental MS disease model is autoimmune encephalomyelitis (EAE), which can be induced in animals by sensitization to myelin antigens (active EAE) or by the transfer of autoreactive T cells (passive EAE). Although the value of the model to MS has been debated, it has allowed the evaluation both of potential MS medications [22] and of the effects of estrogens and progesterone [23–25].

The EAE model is particularly useful for studying autoimmune and inflammatory responses in the CNS. To address myelin repair and neuroprotection more specifically, other experimental *in vitro* and *in vivo* models are available. Thus, the effects of sex steroids on developmental myelination have been studied in cultures of oligodendrocytes and in organotypic cultures of brain slices prepared from neonatal rats or mice [26–28]. The rationale for these studies is that developmental events are recapitulated during myelin repair [29]. However, it is important to keep in mind that the signalling mechanisms involved in myelin sheath formation during development are not always identical to those activated during remyelination in the adult [30]. For this reason, the effects of molecules on myelin repair need also to be investigated in models of demyelination/remyelination in adult animals. Demyelination can be induced by toxins that destroy oligodendrocytes but to some extent spare the axons, such as lysolecithine, ethidium bromide or cuprizone.

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4. Estrogens and progesterone in experimental autoimmune encephalomyelitis

Investigations of the effects of estrogens and progesterone in EAE were driven by the expectation that these hormones would influence disease symptoms by modulating autoimmune and inflammatory processes [25,31]. Thus, most cellular components of the immune system express estrogen receptors (ER) and estrogens can exert either anti- or pro-inflammatory effects, depending on the patho-physiological context [32]. In EAE, estrogens, when administered prior to immunization, delay the onset of symptoms and reduce disease activity. These beneficial effects have been associated with reduced T lymphocyte and macrophage infiltration and a decrease in the production of inflammatory cytokines [23]. Estrogens bind to two nuclear estrogen receptors, ERα and ERβ, but their immunoprotective effects in EAE mainly involve ERα, as they are abrogated in ERα-deficient mice and can be mimicked by ERα-selective ligands [33]. However, the results of a recent study suggest that ethinyl estradiol may slightly reduce the severity of already established EAE by acting on a presumed membrane estrogen receptor [34].

The mechanisms underlying the beneficial effects of estrogens in EAE are still being investigated, but they probably involve a wide range of targets and actions. Estrogen administration has been shown to blunt the production of pro-inflammatory cytokines by T helper type 1 lymphocytes (Th1) and to inhibit expression of the Th1-specific matrix metalloproteinase MMP-9, implicated in CNS infiltration by T cells and monocytes through the blood-brain barrier [35,36]. However, two studies have shown that the protective effects of estradiol on EAE are not necessarily mediated through blood-derived T cells, and point towards an important role for other estrogen-sensitive cellular targets, in the brain [37,38]. Thus, a pivotal role of macrophages and microglia in the modulation of immune responses by estrogens has been demonstrated by cell-specific disruption of estrogen receptors [39]. Importantly, whereas short-term exposure to estradiol decreases the production of inflammatory cytokines by cultured macrophages, their continuous long-term stimulation has the opposite effect [40]. Astrocytes also produce cytokines, chemokines and prostaglandins, and they modulate the function of T-cells; in turn, their neuroinflammatory responses are modulated by estrogens and progesterone [41,42]. In addition to macrophages, microglia and astrocytes, endothelial cells, neurons and oligodendrocytes are potential targets of estrogens [43–45].

Various types of immune cells also express progesterone receptors (PR), thus allowing direct action of the hormone [46]. During pregnancy, progesterone contributes to the establishment of a protective immune environment by modulating multiple immune responses, including a shift away from the production of Th1 pro-inflammatory to Th2 anti-inflammatory cytokines [47]. This regulation of the Th1/Th2 balance by progesterone may play an important role in MS, and may contribute to the improvement of disease symptoms during pregnancy and their post-partum worsening. However, in comparison with the estrogens, the influence of progesterone on EAE has been less well studied. Treating female mice with subcutaneous implants of progesterone starting 1 week before EAE induction attenuated disease severity, and reduced inflammatory responses and demyelination in the spinal cord [24]. Importantly, progesterone also decreased axonal damage and restored the expression of vital neuronal genes [48]. Whereas estrogens may have to be administered prior to the induction of EAE, progesterone treatment initiated as late as 2 weeks after immunization with myelin protein peptide still exerted beneficial effects [49,50]. This observation is reminiscent of the large therapeutic window for the protective effects of progesterone in an experimental model of traumatic brain injury, making progesterone and progestins attractive therapeutic agents [51]. It is, however, interesting to note that synthetic progestins belong to different classes, with distinct pharmacological and biological properties, and not all of them would exert similar neuroprotective effects and be efficient for treating CNS diseases. For instance, the 17alpha-hydroxy-progesterone derivative medroxyprogesterone acetate (MPA), currently used in hormone replacement therapy, increased the severity of EAE and partially reversed the estrogen-induced neuroprotection against glutamate toxicity in neuronal cultures, whereas progesterone or 19-norprogesterone enhanced estradiol-evoked neuroprotection [52,53].

5. The role of estradiol and progesterone in myelination: *in vitro* evidence

Although some EAE studies have reported positive effects of estradiol and progesterone on axons and myelination, it is difficult to distinguish between immunomodulatory and possible neuroprotective and promyelinating actions in these models [48,54]. A role of progesterone in myelination and remyelination has been demonstrated in the peripheral nervous system, where axons are myelinated by Schwann cells [55]. That progesterone also promotes myelin formation by oligodendrocytes in the CNS has been shown in organotypic cultures of cerebellar slices prepared from postnatal rats or mice [27]. Interestingly, the promyelinating effects of progesterone were not observed in cultures prepared from progesterone receptor knockout mice, indicating a key role for the classical intracellular receptors in myelin sheath formation [27]. In the same culture system, it was then shown that progesterone increases the proliferation and maturation of oligodendrocyte progenitor cells (OPC) [28]. This was a significant observation, as successful remyelination in the adult CNS requires the proliferation of OPC and their differentiation into myelinating oligodendrocytes. However, very early progenitor cells are also targets of progesterone. Thus, progesterone stimulates the proliferation of cultured neural preprogenitors via its conversion to allopregnanolone, a potent allosteric modulator of $GABA_A$ receptors. In fact, the mitogenic effect of allopregnanolone is mediated by $GABA_A$ receptors [56]. Estradiol also exerts mitogenic effects on cultured OPC, and oligodendroytes express estrogen receptors [26]. Taken together, these experimental studies suggest that sex steroids may act on oligodendroglial cells at different stages of their maturation, ranging from neural progenitors to mature oligodendrocytes.

6. Estrogens and progesterone in models of toxin-induced demyelination/remyelination

After the demonstration that estradiol and progesterone can influence developmental myelination in cultured cells or slices prepared from neonatal rodent brains, it became necessary to see whether these hormones can also promote myelin repair within the adult CNS. Demyelination has been induced by the stereotaxic injection of ethidium bromide into the caudal cerebellar peduncles of young (10 weeks) and middle-aged (9 months) male rats. In this model, where the rate of myelin repair is age-dependent, progesterone treatment did not affect the rapid remyelination in the young adults, but it did significantly increase remyelination in the older animals [57]. In a model using cuprizone-induced demyelination, treatment of young male mice with estradiol and progesterone (combined) counteracted the loss of myelin by axons in the corpus callosum, but when the hormones were individually administered they had only modest effects [58]. These observations remind us that estradiol and progesterone are in fact hormones acting on their target tissues in a cooperative manner, and that it is important to study their combined actions.

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A recent study examined the effects of progesterone on oligodendroglial cells and myelin in an animal model of spinal cord injury. After traumatic CNS injury, the demyelination of axons is a major contributor to neuron death and loss of function [59]. Following complete transection of the male rat spinal cord, early treatment with progesterone stimulated the proliferation of progenitor cells and their differentiation into oligodendrocytes, and prolonged progesterone treatment promoted the maturation of oligodendrocytes and the synthesis of myelin proteins [60].

7. Sex differences in myelin

Influences of sex steroids on autoimmune and inflammatory responses and their protective and regenerative actions are likely to contribute to the sex differences in the incidence and progress of MS. Indeed, the relevance of sex differences in brain anatomy, chemistry and function to diseases of the nervous system has been increasingly recognized [61]. Thus, in rodents, males have thicker myelin sheaths, greater density of oligodendrocytes and higher myelin protein expression, whereas females show a more rapid turnover of oligodendrocytes [62]. Another important observation is that remyelination in middle-aged rats occurs less efficiently in males than in females [63].

8. Clinical trials of estrogens and progestins in multiple sclerosis

The first clinical study to use sex hormones in women with MS was performed with oral estriol given for 6 months to 10 patients (6 with a relapsing/remitting course and 4 with a secondary progressive course). In the relapsing/remitting patients, the trial was extended after a 6-month post-treatment period with a 4-month retreatment period, during which estriol was used in combination with progesterone to protect against endometrial hyperplasia [64]. In spite of the small number of patients, the researchers concluded that estriol decreased the number and volume of lesions detected by MRI during the treatment periods, and also produced changes in cytokine production by circulating immune cells. Interestingly, when estriol treatment was stopped, lesions increased to pretreatment levels, but when the treatment was reinstituted, they were again significantly decreased [64,65].

In 2005, the double-blind, placebo-controlled POPART'MUS study was launched, the aim of which is to "Prevent Post Partum Relapses with Progestin and Estradiol in MUltiple Sclerosis" [66]. At the time of writing, 171 French and Italian pregnant women with MS had been randomized to take nomegestrol acetate (a synthetic 19-norprogesterone derivative with a high specificity for binding to progestin receptors), combined with a low dose of transdermal 17β-estradiol or placebo pills and patches, immediately after delivery and continuously during the first 3 months post-partum. Clinical follow-up will allow a comparison of the rates of relapse between the treatment and placebo groups. This trial is ongoing, as the aim is recruit a total of 300 women. No serious adverse effects have been reported so far [67].

It is interesting to note that testosterone has also been shown, in a pilot study, to exert a beneficial effect in men with multiple sclerosis [68].

9. Conclusions

Although clinical observations are consistent with an influence of estrogens and progesterone on MS, they have provided insufficient or only indirect evidence. The strongest arguments in favour of hormonal influences on MS are provided by the observed sex differences in the incidence and course of the disease, and by the pregnancy-associated changes in the relapse rate. Changes in MS symptoms related to the menstrual cycle and menopause are not sufficiently documented and require further evaluation. Also, surprisingly little is known about the influence of oral contraceptives or HRT on the course of MS. Taken together, the clinical observations point to a protective effect of hormone treatments, but there is a need for large prospective studies.

In support of the major influences exerted by steroid hormones on MS are the results of experimental animal studies. These have shown that estradiol and progesterone exert multiple beneficial effects on autoimmune responses, neuroinflammation, the viability of neurons, the integrity of axons and the (re)formation of myelin sheaths. To be efficient, MS therapy should target multiple cell types and molecular events, and for this reason combination therapy appears an attractive option [69]. Small neuroactive molecules that exert beneficial actions on different targets in a concerted manner, such as estrogens and selected progestins, could be particularly effective MS treatments. This may lead to new therapeutic indications for steroid compounds already used in contraception or HRT, and in particular for those selectively targeting the intracellular estrogen or progestin receptors. The different synthetic estrogens and progestins are not all equivalent, and only some of them may prove beneficial in the treatment of MS [9,70].

Contributors

All authors contributed equally to this manuscript.

Competing interest

No competing interests.

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