




# Influence of hormones in multiple sclerosis: focus on the most important hormones

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Received: 22 July 2022 / Accepted: 30 November 2022 / Published online: 3 January 2023  
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## Abstract

Hormonal imbalance may be an important factor in the severity of multiple sclerosis (MS) disease. In this context, hormone therapy has been shown to have immunoregulatory potential in various experimental approaches. There is increasing evidence of potentially beneficial effects of thyroid, melatonin, and sex hormones in MS models. These hormones may ameliorate the neurological impairment through immunoregulatory and neuroprotective effects, as well as by reducing oxidative stress. Expanding our knowledge of hormone therapy may be an effective step toward identifying additional molecular/cellular pathways in MS disease. In this review, we discuss the role of several important hormones in MS pathogenesis in terms of their effects on immunoregulatory aspects and neuroprotection.

**Keywords** Multiple sclerosis · Thyroid hormone · Melatonin · Steroid hormone

## Introduction

Multiple sclerosis (MS) is a multifactorial disease in which environmental, genetic, and epigenetic factors may play causal roles and interact with modifiable risk factors. However, some other fundamental aspects of disease

etiopathogenesis remain to be elucidated (Thompson et al. 2018). According to the latest edition of the MS Atlas, the number of MS patients worldwide is expected to increase to 2.8 million by 2020, 30% more than in 2013 (Walton et al. 2020). The above reasons, including the increasing prevalence/incidence of MS, the complex etiology, and the significant economic burden, necessitate a continued quest to understand this disease (Tobore 2020). To counteract the central nervous system (CNS) damage in MS, one of the ideal treatments is to promote remyelination, which could reduce the severity of the disease (Lubetzki et al. 2020). Several studies suggest that hormones from body glands play an important role in the mechanism of immune/CNS cells (Ysraelit and Correale 2019; Deckx et al. 2013). In this context, there is increasing evidence of the beneficial functions of several important hormones (e.g., thyroid, melatonin, and sex hormones). There are numerous data suggesting that thyroid hormones (TH) might protect the CNS through immunoregulatory effects. Such a reduction in inflammatory responses was shown in a gradual reduction of CD45<sup>+</sup> microglial cells, interferon-gamma (IFN- $\gamma$ ), and interleukin-10 (IL-10) after TH therapy in the experimental models (Payghani et al. 2017; Harsan et al. 2008).

Excessive neuroinflammation and oxidative stress have potentially negative effects on biological energy and may lead to axonal degeneration in patients with advanced MS

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(Pegoretti et al. 2020). Melatonin can inhibit free radicals, intracellular reactive oxygen species (ROS), and thus inflammation by forming antioxidant enzymes and reducing the production of proinflammatory cytokines (e.g., tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , and IL-6). Therefore, it acts as a potent antioxidant and anti-inflammatory agent (Tan et al. 2016; Eghbal et al. 2016).

There are prevalence differences between the sexes in autoimmune diseases such as MS, (Ysrraelit and Correale 2019) and the most frequent relapses of MS occur in women (Kamel 2019). Studies show that during pregnancy, placental hormones such as estriol (E3) can reduce the severity of MS by regulating immune cell function. Steroid hormones play a fundamental role in suppressing the immune system and inhibiting immunological responses by controlling leukocyte migration, altering macrophage polarization, and inducing T cell apoptosis (Shimba et al. 2021). Overall, this review aims to provide an overview of the main hormonal effects in MS treatment and the associated challenges of hormonal imbalance and hormone therapy.

## MS: a disorder of myelination

MS is primarily an inflammatory disease of the brain and spinal cord in which localized lymphocytic infiltration leads to the destruction of myelin and axons (Azimzadeh et al. 2021; Eslami et al. 2020). In MS patients, myelinated axons may be degraded over time due to a lack of spontaneous remyelination, making delayed differentiation of oligodendrocyte precursor cells (OPCs) (Trapp and Nave 2008; Azimzadeh et al. 2020). Cortical MS lesions were categorized based on their localization. In type I lesions, demyelination occurs at the leukocortical border. Partial perivascular demyelinated areas are evident in type II lesions, and extensive subpial demyelinated plaques in layers III or IV are termed to as type III lesions. Although there is no apparent relationship between lesion location and disease progression, cortical damage is associated with motor/sensory deficits and contributes to cognitive/executive dysfunction which the typical neurological deterioration seen in MS patients (Dutta and Trapp 2011; Rinaldi et al. 2010; Vucic et al. 2012). Remyelination is a complex process that requires not only sufficient numbers of oligodendrocytes but also precise placement (Albornoz et al. 2013). Oligodendrocytes specifically promote the structural and metabolic integrity of CNS neurons. On the other hand, the damaged axons and the reduced potential of the myelin sheath are due to the loss of this support. Neurons have the highest metabolic demand; therefore, their active axons are particularly vulnerable when electrical activity is high. Indeed, axonal injury and poor myelin sheathing can lead to delayed communication at synapses, increasing the brain's susceptibility to overt

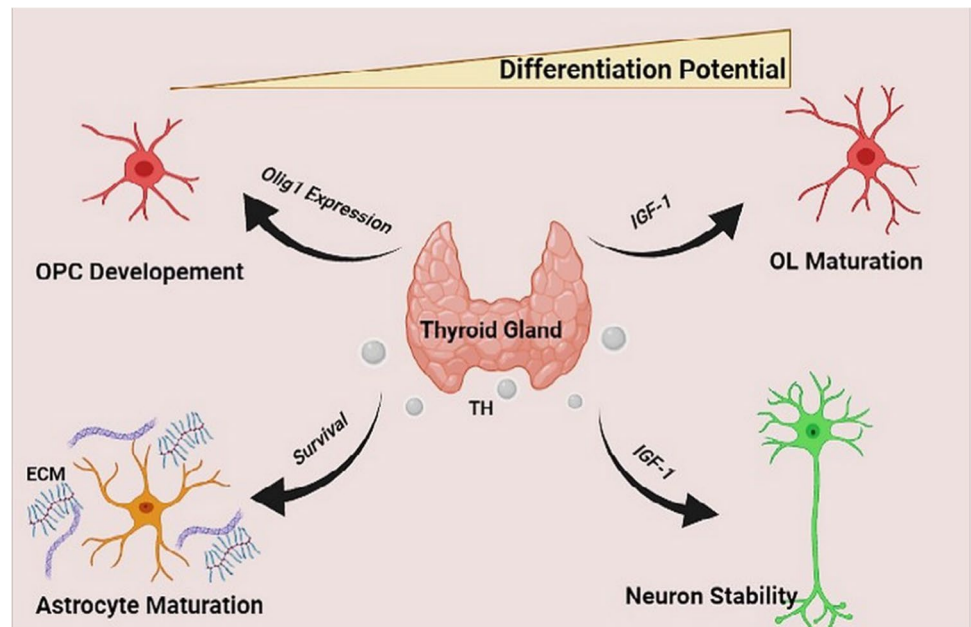
neurodegeneration (Saab et al. 2013). Sufficient remyelination at the appropriate time is still considered the most effective strategy to alleviate MS. First, immune regulation alone is not sufficient to treat chronic neurological impairment, although lesion regeneration appears to be successful in MS (Michailidou et al. 2015). Second, MS impairment increases with age, whereas the ability to remyelinate decreases with age. Therefore, early promotion of remyelination is crucial (Brugarolas and Popko 2014). It is hypothesized that promoting remyelination and neuroprotection may be of great benefit in MS (El-Akabawy and Rashed 2015; Brown et al. 2014).

## Thyroid hormones

### Thyroid hormones and remyelination

Thyroid hormones (TH) act via nuclear receptors on several steps of oligodendrocyte development/myelination and play a positive role in normal myelination (Schoonover et al. 2004; Pagnin et al. 2021). In the presence of a mitogen, TH help OPCs trigger effector mechanism, including disruption of cell division and initiation of differentiation (Tokumoto et al. 2001). TH play an essential role in regulating the maturation of oligodendrocytes, the activation of OPCs, and the protection of the myelin sheath. In addition, TH protect the CNS through immunoregulatory effects, including the gradual reduction of CD45<sup>+</sup> microglial cells, IFN- $\gamma$  reduction, and IL-10 stability following T3 treatment in mice (Harsan et al. 2008; Payghani et al. 2017). Indeed, there are several approaches to TH-induced remyelination, such as increasing neurotrophic factors, stimulating oligodendrocyte production, and suppressing apoptosis (Marzali et al. 2015; Picou et al. 2012). Control of neurogenesis through the production of extracellular matrix proteins and growth factors to regulate astrocyte maturation, as well as expression of cytoskeletal proteins during axon growth and involvement in axon/oligodendrocyte interactions are other well-established functions of TH (Trentin 2006; Mohácsik et al. 2011; Talhada et al. 2019; Zendedel et al. 2016). In this regard, TH administration could increase the expression of the transcription factor Olig1 in the optic nerve and induce new OPCs. Similarly, TH restore the ability of mature oligodendrocytes to induce MBP and limit axonal damage in the white/Gy matter of the experimental autoimmune encephalomyelitis (EAE) model (Fernandez et al. 2004) (Fig. 1). In addition, some studies have pointed out the indirect effects of TH on remyelination. For example, it has been suggested that the beneficial effect of TH on MS pathophysiology may be due to its effects on growth hormones and their effectors (e.g. insulin-like growth factor (IGF-1)) by promoting neuron/oligodendrocyte survival and myelination process (Akcali

**Fig. 1** The thyroid hormones affect CNS remyelination. TH; Thyroid Hormones, OPC; Oligodendrocyte Precursor Cell, OL; Oligodendrocyte, ECM; Extracellular Matrix, Olig1; Oligodendrocyte Transcription Factor 1, IGF-1; Insulin Growth Factor



et al. 2017). Harsan and colleagues applied a multidimensional technique to evaluate the effects of TH on endogenous stimulation of neuronal repair mechanisms in mice treated long-term with cuprizone. A significant loss in the subventricular zone (SVZ) and corpus callosum was reversed by TH treatment. It was also found that TH can promote the formation of OPCs and other stages of the oligodendrocyte lineage in chronic demyelination. In other words, TH treatment provides a favorable environment for the development of OPCs and regulates their differentiation (Harsan et al. 2008). These findings have been repeatedly confirmed in other studies (Castelo-Branco et al. 2014; Chaudhary et al. 2021; Zhang et al. 2015); Silvestroff et al. demonstrated that cortical lesions may also benefit from TH treatment by accelerating the cortical remyelination rate in Wistar rats after cuprizone intoxication (Silvestroff et al. 2012).

### Is a TH agonist a potential therapeutic candidate for MS?

Current literature suggests that TH employ multiple mechanisms to combat MS progression, including regulation of extracellular glutamate and matrix metalloproteinase 9 (MMP-9) expression as well as regulation of vitamin D levels and oxidative stress (Tobore 2020). TH agonists (selective thyromimetic) have the potential to bind to the TH receptor (TR). Sobetirome, eprotrirome, and resmetirom are just a few of the TR-selective T3 analogs that have been developed in the last two decades and has been shown to provide much of the therapeutic benefits of T3 without the negative side effects (Saponaro et al. 2020). Sobetirome is a selective thyromimetic with minimal side effects associated

with hyperthyroidism and one of the few thyromimetic that cross the blood-brain barrier (BBB) and reach the CNS (Ferrara et al. 2017; Placzek et al. 2016). Sob-AM2, a CNS-selective prodrug of sobetirome, has been noted to support myelin regeneration. This effect has been associated with significant improvement in neurological clinical symptoms associated with demyelinating CNS diseases.

## Melatonin

### Antioxidant aspects of melatonin

Melatonin has a small, amphiphilic, and nonpolar molecular structure derived from the amino acid. It is secreted mainly by the pineal gland into the blood or cerebrospinal fluid and is important as an antioxidant in neurological diseases (Alghamdi 2018). Melatonin exerts multifunctional activities in various tissues (membranous or cytoplasmic) through receptor-dependent or receptor-independent mechanisms (Slominski et al. 2012). It deactivates free radical molecules and the hydroxyl anion radical, resulting in a cyclic 3-hydroxy-melatonin derivative that is excreted via the kidneys (Reiter et al. 2018). In *in vivo/vitro* models, anti-carcinogenic effects of melatonin have been reported, particularly in estrogen-responsive breast tumors (Menéndez-Menéndez and Martínez-Campa 2018).

Pathological circumstances characterized by an unfavorable balance of free radicals and elimination mechanisms lead to “oxidative stress,” which increases oxidative damage to biomolecules (Sharifi-Rad et al. 2020). The CNS is extremely vulnerable to oxidative stress due to its increased

oxygen consumption, which can increase the production of ROS. Melatonin is known to be a potent antioxidant in diseases associated with oxidative stress (e.g., MS, Alzheimer's disease, and cancer). In addition, its protective effects including improving remyelination, mitochondrial function, and reducing inflammation in experimental MS models (e.g. IL-1, TNF) have attracted wide attention (Ghareghani et al. 2019). Melatonin directly inhibits mitochondrial dysfunction and ROS production (Kashani et al. 2014; Reiter et al. 2020). Furthermore, specific enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione reductase (GR), and glutathione (GSH) are less abundant in the CNS than in other parts of the body (Salim 2017). Indirectly, melatonin as an antioxidant increases the function of these important enzymes (Adamczyk-Sowa et al. 2014) (Fig. 2). Notably, excessive neuroinflammation and oxidative stress have irreversible effects on biological energy. In advanced MS patients, the process that requires energy can be disrupted and lead to axonal degeneration. In particular, inhibition of demyelination and promotion of the enriched environment (ENR) process by adult oligodendrocytes may be effective in the treatment of MS (Kremer et al. 2019). Therefore, the balance between ROS production and the antioxidant activity of enzymes prevents the oxidative stress and increases mitochondrial function (Adamczyk and Adamczyk-Sowa 2016).

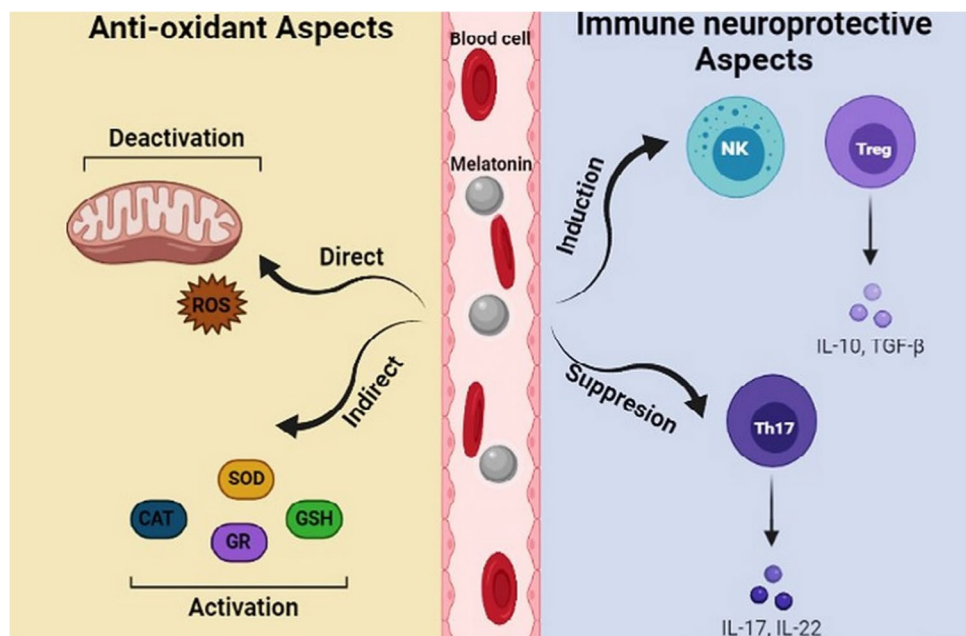
### Anti-inflammatory effects of melatonin

There is a growing body of data suggesting that the overproduction of pro-inflammatory cytokines, ROS, and nitrogen species (e.g. nitric oxide, hydrogen peroxide, peroxynitrite, and hydroxyl radicals) as a result of T cell, macrophage,

and astrocyte activity may be toxic to oligodendrocytes by contributing to demyelination in response to inflammatory stimuli (Wen et al. 2016; Li et al. 2011; Solleiro-Villavicencio and Rivas-Arancibia 2018). In vivo administration of high doses of melatonin stimulated the immune system by increasing regulatory T cell activity (Treg), triggering numerous humoral responses, and preventing age-related thymic involution (Shomali et al. 2021). In this context, a previous study by Pierpaoli and colleagues found that melatonin administration in vitro increased Treg/natural killer (NK) cells activity and IL-2/IFN- $\gamma$  production in human monocytes (Pierpaoli and Regelson 1994). Melatonin could exert its therapeutic effects by increasing IL-10 levels in Treg cells and suppressing Th17 cell differentiation (Fig. 2). However, there is evidence that NAS (N acetyl serotonin) may be more effective than melatonin in the treatment process due to its better inhibitory effect on Th17 differentiation (Chen et al. 2016). During the relapse phase of MS, CD44 expression increases in circulating T cells. Melatonin has been shown to suppress CD44 expression in T-effector cells while increasing CD44 expression in Treg cells (Ren et al. 2017).

The low dose of melatonin serum levels and clinical signs (e.g. fatigue and sleep disturbance) of MS patients may indicate that melatonin could play an important role as a hormone candidate in MS therapy (Damasceno et al. 2015). In a randomized, placebo-controlled study, 36 individuals with RRMS were treated with interferon beta-1b (IFN $\beta$ -1b). The study aimed to find out how well melatonin affects serum pro-inflammatory cytokines and oxidative stress indicators in patients with MS. Melatonin (25 mg/d) was administered orally to the experimental group for 6 months. Thereafter,

**Fig. 2** Two main aspects of melatonin hormone function: Anti-oxidant and Immune neuroprotection. NK; Natural Killer, Treg; Regulatory T cell, Th17; T helper 17, IL; Interleukin, ROS; Reactive Oxygen Species, SOD; Superoxide Dismutase, CAT; Catalase, GR; Glutathione Reductase, GSH; Glutathione





pro-inflammatory cytokine levels and oxidative stress markers were substantially decreased, suggesting that 6 months of melatonin treatment helps to reduce serum concentrations of pro-inflammatory cytokines and oxidative stress indicators in RRMS patients (Sánchez-López et al. 2018). Unexpectedly, a high dose of melatonin appears to have a pro-inflammatory effect (Escribano et al. 2022). However, these results encourage further research on the safety and efficacy of melatonin administration in MS patients. Moreover, gender might influence melatonin function during the remyelination phase. For example, male mice had a protective effect after melatonin treatment, whereas female mice showed no effect. These results suggest a complicated interplay between melatonin, remyelination, and sex hormones (Taleb and Alghamdi 2020).

## Sex hormones

### Imbalance of sex hormones in MS

Steroid hormones (divided into corticosteroids and sex steroids) can be evaluated from different points of view, of which “sexual dimorphism” in MS and corticosteroids as first-line therapy for relapses can be mentioned (Adhya et al. 2018; Ozakbas et al. 2017; Frye 2009). MS incidence is more common in young women (20–40 years). In fact, distinct sex differences include earlier disease onset in women and more frequent relapses in men, faster disease progression, and poorer prognosis in women (Coyle 2021). Genetically, sex is not the main factor, suggesting that environmental influences (e.g. unbalanced lifestyle, contraceptive use) contribute to a higher MS risk in women (Ysraelit and Correale 2019). Puberty, pregnancy, puerperium, and menopause are all hormone-related physiological states in women that have a major impact on MS prevalence and prognosis. Therefore, hormonal and genetic variables are thought to play a key role in disease progression (Ysraelit and Correale 2019). MS patients are more likely to suffer from physical disability during the premenstrual period than during the ovulatory period (Wingerchuk and Rodriguez 2006). Similarly, there are no sex differences in MS before puberty, although there is evidence that the age of menarche may be associated with the age of onset, further linking sex hormones to MS risk in childhood and adolescence (Jiang et al. 2018; Salpietro et al. 2018; Chitnis 2013).

The discovery of a decrease in relapse rates in women with MS during pregnancy has led to an increase in data supporting the anti-inflammatory effect of estrogens in MS, although the molecular mechanisms are still unknown (Simone et al. 2021). However, Rossi et al. (2018) mentioned that an increase in amino acid (AA) catabolism could be one of the reasons for autoimmunity prevention during

pregnancy, which significantly decreases in the postpartum period (McGaha et al. 2012). In the postpartum period, there is a significant increase in relapse rates due to a sudden decrease in estrogen, progesterone, and glucocorticoids levels and a rapid return to pre-pregnancy immunological function (Abu-Raya et al. 2020). Indeed, the postpartum state has been described as an immune reconstitution-like inflammatory phenomenon caused by the comeback of pro-inflammatory cellular activity as a result of fetal/placental birth (Finkelsztejn et al. 2011). At the same time, the increase in hormones involved in breastfeeding processes triggered during this period may potentially contribute to increased disease activity (de Souza Costa et al. 2016). Little is known about the effects of menopause/andropause and hormone replacement therapy (HRT) on MS progression (Miller et al. 2014). Any consequences of hormonal changes during menopause/andropause may be masked by age-related changes in MS disease (Kim et al. 2021; Midaglia et al. 2020). For example, follow-up of patients with late-onset MS (beyond the age of 40) (LOMS) and young onset MS (18–40 years) (YOMS) found that male sex and older age had shortened time to EDSS 6.0 (Alroughani et al. 2016). It appears that andropause along with older age, has a stronger impact on MS progression compared with menopause (Fig. 3). However, MS incidence is higher in female LOMS patients (Naseri et al. 2021).

### Immunoregulatory effects of sex hormones on MS

Knowing the immunoregulatory effect of sex hormones on MS, Benedek et al. undertook a concerted effort to elucidate an aspect of estrogen-induced immune regulation in EAE in which regulatory B cells were supported by estrogen-treated M2 macrophages in a feedback loop (Benedek et al. 2017b). In addition, the group investigated the effect of estrogen on gut microbiota composition in EAE mice and associated

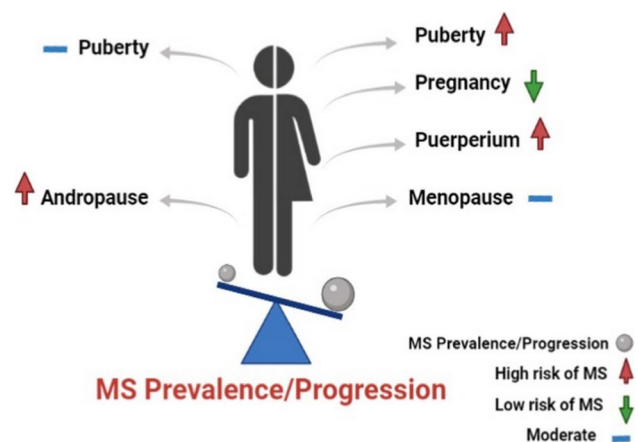


Fig. 3 MS prevalence/progression diagram in men and women

immune regulation (Benedek et al. 2017a). They found that estrogen prevented EAE-associated inflammation and could improve the immune regulation. Lanello et al. demonstrated that Th17 and Treg cell type-specific regulatory regions (CSRs) are controlled by estrogen receptor alpha (ER $\alpha$ ). These CSRs were detected in polarized Th17 cells from healthy donors (HD) and in peripheral blood mononuclear cells, Th17, and Treg cells from MS patients during pregnancy (Iannello et al. 2019). Overall, estrogen is thought to immunomodulate the epigenome of CD4<sup>+</sup> T cells in MS; the discovered CSRs could be used as biomarkers to track disease progression or as novel treatment targets.

The pregnancy hormone estradiol may improve innate immune cell function by regulating Treg/Th17 balance, inhibiting neutrophil phagocytic activity, increasing indoleamine-2,3-dioxygenase (IDO) activity, decreasing IL-17-producing NK cells, and may play an indispensable role in the development of immune tolerance in the pathogenesis of MS (Nekrasova and Shirshv 2020; Robinson and Klein 2012). Neurosteroids are subtype steroids synthesized by CNS cells (e.g. oligodendrocytes, astrocytes, and microglia) to enhance myelination and anti-inflammatory effects. Decreased expression of the neurosteroids and related enzymes leads to increased expression of pro-inflammatory factors, oxidizing enzymes, and ultimately demyelination (Panzica et al. 2012; Porcu et al. 2016; Leicaj et al. 2018). Further investigations are needed to evaluate the major mechanisms of neurosteroids.

## Conclusion

Hormonal dysfunction plays a fundamental role in the pathogenesis of MS disease. The beneficial effects of the most important hormones including thyroid, melatonin, and sex hormones are well-defined in MS experimental models. Besides, these hormones may ameliorate neurological impairment through immunoregulatory and neuroprotective effects, as well as by reducing oxidative stress. Especially, hormone therapy could improve immune system function (e.g., regulation of Treg/Th17 balance, inhibition of phagocytic activity, reduction of NK cells, and development of immune tolerance) in MS pathogenesis. However, the new window/mechanism between hormones and CNS cells in MS therapy needs to be deciphered. In conclusion, expanding the knowledge of hormone therapy may be an effective step towards identifying further molecular and cellular pathways.

**Authors' contribution** A.S, S.G: Wrote the manuscript. Z.M: Contributed to the literature search and editing of the manuscript. N.M, Z.K, T.S: Revised the manuscript. M.A: Supervised the manuscript preparation. All authors have read and agreed to the published version of the manuscript.

**Data availability** Not applicable.

**Code availability** Not applicable.

## Declarations

**Ethics approval** This article contains no original data from studies with human participants or animals performed by any of the authors, apart from the data already published and quoted herein.

**Conflicts of interest/Competing interests** The authors declare that they have no conflict of interest.

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