Review

Hormonal regulation of oligodendrogenesis II: implications for myelin repair

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Abstract: Alterations in myelin, the protective and insulating sheath surrounding axons, affect brain function, as is evident in demyelinating diseases where the loss of myelin leads to cognitive and motor dysfunction. Recent evidence suggests that changes in myelination, including both hyper- and hypo-myelination, may also play a role in numerous neurological and psychiatric diseases. Protecting myelin and promoting remyelination is thus crucial for a wide range of disorders. Oligodendrocytes (OLs) are the cells that generate myelin, and oligodendrogenesis (OLgenesis), the creation of new OLs, continues throughout life and is necessary for myelin plasticity and remyelination. Understanding the regulation of OLgenesis and myelin plasticity within disease contexts is therefore critical for the development of novel therapeutic targets. In our companion manuscript [1], we review literature demonstrating that multiple hormone classes are involved in the regulation of OLgenesis under physiological conditions. The majority of hormones enhance OLgenesis, increasing oligodendrocyte precursor cell differentiation and inducing maturation and myelin production in OLs. Thus, hormonal treatments present a promising route to promote remyelination. Here, we review literature on hormonal regulation of OLgenesis within the context of disorders. We focus on steroid hormones, including glucocorticoids and sex hormones, peptide hormones such as insulin-like growth factor 1, and thyroid hormones. For each hormone, we describe whether they aid in OL survival, differentiation, or remyelination, and we discuss their mechanisms of action, if known. Several of these hormones have yielded promising results in both animal models and in human conditions; however, a better understanding of hormonal effects, interactions, and their mechanisms will ultimately lead to more targeted therapeutics for myelin repair.

Keywords: oligodendrogenesis, remyelination, hormones, steroids, peptides

1. Introduction

Many neurological disorders are characterized by a change in myelin including psychiatric disorders, Alzheimer's Disease (AD) and of course, demyelinating disorders [2–5]. By definition, demyelinating disorders are conditions in which myelin, the protective and insulating sheath surrounding axons, is damaged and ultimately lost. In addition to its canonical role in saltatory conduction, myelin has been increasingly implicated in a wide range of central nervous system (CNS) functions, such as neural synchrony, synaptic function, and trophic support of myelinated axons [6–8]. As a result, extensive myelin loss can be accompanied by a host of secondary pathologies, including axonal degeneration, that lead to irreversible deficits in cognition and motor function [9–11]. Disorders characterized by white matter loss, including demyelinating disorders, are

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highly prevalent, with multiple sclerosis (MS) alone affecting more than 1 in 500 individuals [12]. Currently, there are no cures and few therapeutic options for demyelinating conditions. Thus, understanding the mechanisms to preserve myelin and promote remyelination is critical to the development of new and effective treatments.

Oligodendrocytes (OLs) are the glial cells in the CNS that generate the myelin sheath. Once mature, these cells may have a dramatically limited capacity for creating new myelin [13–15]. In addition, injury, inflammation, and myelin damage can lead to widespread OL cell death [16–19]. As a result, oligodendrogenesis (OLgenesis), the creation of new OLs, is crucial for remyelination following injury (Figure 1) [20–22]. Remyelination, however, is often impaired in demyelinating disorders, which may be due to deficits in OLgenesis [23]. For example, in MS patients, oligodendrocyte precursor cells (OPCs) are compromised in their ability to differentiate into mature, myelinating OLs [24]. Understanding the mechanisms of both normal and altered OLgenesis and subsequent myelination is important not only for disorders such as MS, but also for all disorders characterized by changes in CNS myelination, including spinal cord injury (SCI), stroke, AD, post-traumatic stress disorder (PTSD), and other psychiatric disorders [2,4,5,25–27].

The mechanisms underlying the process of remyelination can be investigated in animal models that replicate some aspects of human pathologies. The most commonly used animal model for MS is experimental autoimmune encephalomyelitis (EAE), which involves the induction of an immune response to myelin antigens. This leads to the progressive loss of myelin, as well as cognitive and motor deficits [28,29]. In addition, acute or chronic demyelination can be triggered by toxins such as lysophosphatidylcholine (LPC) and cuprizone, which induce local inflammation or directly induce OL apoptosis, respectively [30,31]. Lastly, physical injury, as observed in SCI, and hypoxia, either induced directly or as a result of ischemia, have been used in controlled laboratory settings to induce myelin loss [32,33]. Collectively, these animal models allow us to test the factors and cellular mechanisms, both *in vitro* and *in vivo*, that may progress myelin pathology or that conversely, may aid in myelin repair.

OLgenesis is regulated by numerous endogenous factors, including many different hormones (for a detailed review, see [1]. In fact, MS, the most common demyelinating disorder, is almost three times more common in women than in men, suggesting that sex hormones may play a role in disease pathology [12]. In addition, women with MS often have fewer relapses during pregnancy, at a time when sex hormones and peptide hormones like prolactin (PRL) are at their peak [34]. Many hormones, including insulin-like growth factor 1 (IGF-1), thyroid hormones (THs), and steroid hormones, also influence OLgenesis during development and throughout adulthood. Hence, understanding hormonal effects on OLgenesis and remyelination in models of myelin pathology provides an avenue for ultimately improving myelin repair.

In this review, we will explore how hormonal factors affect OLgenesis within disease contexts. The accompanying review [1] introduces the hormones discussed, and explores hormonal regulation of OLgenesis under physiological conditions. As in our companion review, here, we will again restrict our discussion to the "classic" endocrine signalling molecules, which are typically released from a gland into circulation to act upon distant tissues. We will describe the effects of classic steroid hormones, peptide hormones such as IGF-1, and thyroid hormones, among others. For each category, we will note the hormone's effects on animal models characterized by impaired myelination, and we will discuss their relevance to findings in human disorders. While most of the literature we review is focused on demyelinating disorders, we also note relevance for additional diseases. We end with a discussion of future directions. Overall, we advocate for more extensive research into hormones as a potential therapeutic target for myelin repair.

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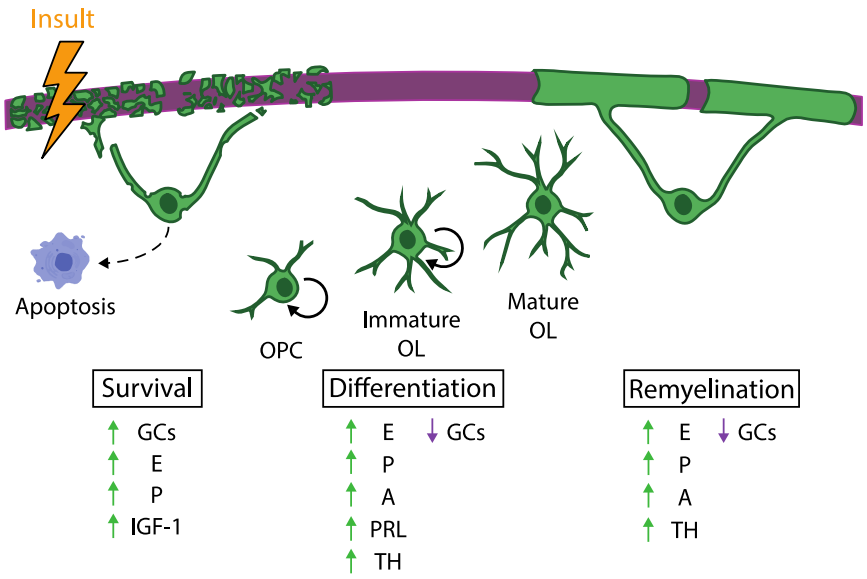

Figure 1. After an insult that leads to myelin degradation, OL survival, OLgenesis, and remyelination are differentially affected by various classes of hormones. Green arrow = promote, Purple arrow = downregulate. GCs = glucocorticoids, E = estrogens, P = progestogens, A = androgens, IGF-1 = insulin-like growth factor-1, PRL = prolactin, TH = thyroid hormones

2. Steroid Hormones

Steroids are hydrophobic molecules synthesized from cholesterol that have important actions within the CNS, including regulation of OLgenesis [1]. For this review, we will focus on a subset of steroid hormones synthesized primarily in the adrenal cortex and gonads, namely the stress and sex hormones, which canonically act through nuclear receptor signaling [35,36]. As we describe in our companion review, under physiological conditions, steroid hormones act to increase OPC differentiation and enhance maturation/myelination of OLs [1]. In line with their effects on OLgenesis, stress hormones such as glucocorticoids, and sex hormones such as estrogen, progesterone, and testosterone (T), are associated with MS and other myelin related diseases and may aid in some aspects of myelin repair [37–39].

2.1. Glucocorticoids

Glucocorticoids (GCs) are the primary stress hormones. This family includes endogenous cortisol (the primary GC for humans), corticosterone (Cort; the primary GC for rodents), and synthetic hormones such as dexamethasone (Dex). Like many steroid hormones, GCs have been shown *in vitro* and *in vivo* to enhance OLgenesis, specifically by enhancing differentiation of neural stem cells (NSCs) and OPCs, via activation of glucocorticoid receptors (GRs) [1,40], and ultimately increasing expression of myelin basic protein (MBP) [41,42]. Yet, prolonged exposure to Cort or Dex can also reduce myelination, indicating the effects of GCs may depend on dosing and duration [43]. It is important to note that in disease states, particularly autoimmune diseases such as MS, GC hormones can affect myelination either by directly activating GRs in OPCs and OLs to modulate proliferation, differentiation, survival or myelination rate, or indirectly, through GCs modulation of immune functions.

Implications for disorders:

Levels of circulating GC hormones can be increased by stress, injury, and disease, and although prolonged or high levels of GCs may be harmful, acute increases in GCs may in fact be beneficial. Several studies have sought to characterize a role for GCs as a potential treatment for disorders involving white matter injury, including MS and SCI,

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and are often given for their anti-inflammatory properties. For example, methylprednisolone (MP), a synthetic GR agonist often given to spinal cord patients within a few hours of injury, protects against OL cell death following SCI in mice; specifically, MP treatment after SCI increases the number of mature OLs at the site of injury eight days later [44]. This protective effect was unique to OLs and was dependent on GR signaling [44]. In a similar study, MP was found to protect against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-induced excitotoxicity, an effect that was causally related to its upregulation of the neuroprotective cytokine erythropoietin [45]. In addition to effects on OL survival, MP also affects OPC proliferation. Specifically, MP treatment reduced the number of proliferating neural progenitor cells (NPCs) and OPCs labeled 1-6 days after SCI, calling into question whether MP is beneficial for myelin repair. This effect was only observed in the short term; MP did not affect OPC proliferation one month after injury [46]. Yet, this study did not address whether a reduction in OPCs was due to increased differentiation into mature OLs, which would in fact aid in injury recovery.

In animal models of demyelination, GCs have been noted to be protective against OL and myelin loss by preventing inflammatory cytokine-induced OL apoptosis. Specifically, the synthetic GC prednisone, which is often given to MS patients for its anti-inflammatory properties, alleviates demyelination and inhibits inflammatory cytokines and signaling pathways [47]. Furthermore, GCs protect OPCs and OLs from pro-inflammatory cytokine- (INF_{γ} and TNFα) induced cell death [48,49]. OL apoptosis, often induced by inflammation, is important in MS as well as other demyelinating disorders [9,50,51]. Future work should aim to determine if GC protection from cell death is mediated by GC's immunosuppressive effects or directly by GC action on OLs.

Despite this evidence for prevention of OL loss, there is conflicting evidence of whether GCs can enhance remyelination in an injury or disease context. While GCs such as Dex and MP accelerate OPC differentiation in culture, GCs impair remyelination in the corpus callosum *in vivo* [52]. Thus, while GCs can push OLs to mature, this enhanced maturation does not always correspond with enhanced myelination, and GCs might in fact impair remyelination *in vivo*. More research is needed to test how GCs affect OL development and myelination, particularly in injury and disease models. In addition, *in vivo*, GCs act in concert with other hormones, and such interactions may drive different outcomes of OLgenesis and myelination. For example, Dex down-regulates expression of IGF-1, the IGF-1 receptor, and IGF-1 binding proteins [53]. Thus, exposure to high levels of GCs could have a negative impact on OLgenesis by impairing the action of otherwise pro-OL hormones like IGF-1. Such hormonal interactions will be important to consider in disease models *in vivo*.

Understanding how GCs affect OLgenesis has important broader implications not only for demyelinating disorders, but also for human disorders characterized by alterations in the Hypothalamic-Pituitary-Adrenal (HPA) axis and changes in cortisol, including post-traumatic stress disorder (PTSD) and depression [54,55]. Interestingly, these disorders are also associated with changes in myelin [26,56] (see Box 1), and GCs may provide one mechanism by which these alterations arise. For example, in patients with major depressive disorder, elevated cortisol is correlated with reduced white matter integrity in fronto-subcortical and fronto-limbic systems [57]. In our own work using animal models, we recently identified sex-, age- and region-sepcific changes in OLs and myelin following exposure to acute trauma. Juvenile exposure to acute stress led to long-lasting reductions in grey matter myelin in female, but not male, adult rats [58]. In addition, male rats demonstrated short term changes in myelin content; these changes were associated with Cort levels during stress exposure [58]. Furthermore, in adult male rats exposed to the same stressor, hippocampal and amygdala myelin levels positively correlated with avoidance and fear scores, respectively [59]. Yet, more research is needed to identify a causal role for GCs in altering OLs and myelin in stress-associated disorders.

Box 1: Alterations of myelin in stress-related neuropsychiatric disorders:

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Many neuropsychiatric disorders are characterized by alterations in myelin, both in white matter and grey matter regions [2,26,60]. White matter (WM) myelin is composed primarily of bundles of myelinated axons, while grey matter (GM) myelin is less dense, with myelinated axons closer to cell bodies and dendrites [61]. Alterations in myelin have been implicated specifically in a number of stress-related mental health disorders, including depression and PTSD, suggesting myelin, and the OLs that generate it, might play a functional role in mood [26,60,62–67]. For example, depression patients demonstrate reduced WM integrity and intensity across many brain regions, especially in areas such as the prefrontal cortex [60,65,67,68]. These alterations in myelin may occur through decreases in OL density, expression of OL related genes, and/or changes in OL morphology, all of which have been observed in depression [60,69]. Intriguingly, changes in WM in the fronto-limbic system may correlate with behavioral symptoms of depression such as rumination [70].

Alterations in WM myelin are also observed in PTSD patients, with reductions in WM volume in many areas, yet increases in others, highlighting the regional heterogeneity of trauma's impact on myelin [71]. In addition to changes in WM, PTSD patients demonstrate alterations in GM myelin; veterans with PTSD have increased hippocampal GM myelin content compared to trauma-exposed controls and interestingly, this increase in hippocampal myelin positively correlates with PTSD symptom severity [26]. In a recent study, changes in WM myelin were also found to positively correlate with PTSD symptoms [72]. Altogether, more work will be needed to piece apart regional changes in WM and GM myelin in these stress-induced disorders, as well as the underlying mechanisms by which alterations in myelin arise. Finally, the studies we describe here only scratch the surface of a rich field of literature.

2.2. Sex Hormones

Sex hormones, including the estrogens, progestogens, and androgens, all modulate OLgenesis and myelogenesis, as we describe in our companion review [1,73,74]. Indeed, males and females are differentially affected by demyelinating disorders such as MS [12], and differences in sex hormones might account for some of this sex-specific risk.

2.2.1. Estrogens

Estrogen, the major female sex hormone, is produced primarily by the ovaries. The most potent estrogen, 17-β estradiol (E2), has many physiological functions for both male and female animals, including regulation of OLgenesis [1]. Broadly, E2 promotes OPC differentiation and OL maturation, acting through its two nuclear estrogen receptors (ERs), ERα and ERβ, and through its membrane bound receptor GPR30, all of which are found on OLs [75–80].

Implications for disorders:

Estrogen treatment may have protective and rehabilitative properties for OLs, with important implications for demyelinating disorders. Indeed, estrogen treatments improve clinical outcomes for MS patients, and are now ready for phase 3 clinical trials [81–83]. In animal models, E2 protects against hypoxia/ischemia and SCI-induced OL cell death and white matter damage [84,85]. Estradiol also promotes remyelination and reduces the loss of OLs in MS models and following cuprizone-induced demyelination [86,87]. For example, in an animal model of EAE, an E2 agonist increased both the number of OLs as well as axon myelination [88]. Thus, estrogens aid in OL survival and promote remyelination following injury. These protective and pro-myelinating effects may occur through several estrogen-receptor mediated mechanisms. In immature and mature OLs, E2 decreases the cytotoxic effect of free radical donors, which are implicated in OL damage and MS pathology[89,90]; this protective effect was blocked by an ER agonist [79].. Binding of ERβ also activates the Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT)/Mammalian Target of Rapamycin (mTOR) signaling pathway in OLs,

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thereby promoting OL survival and axon remyelination [91]. Activation of the membrane-bound GPR30 receptor also contributes to improved remyelination in cuprizone-induced demyelination models [92]. In both the spinal cord and in the corpus callosum, a specific GPR30 agonist elicits both increased OPC proliferation and maturation, prompting OPCs to develop into immature OLs. Further, animals treated with GPR30 agonists showed increased MBP immunoreactivity and thicker axon diameters [92].

In addition, estrogen's aid in remyelination may occur, in part, via interactions with other hormones. For example, in cuprizone-induced demyelination models, E2 induces production of IGF-1 by astrocytes, which in turn promotes OL proliferation and differentiation [93]. In addition, interestingly, estrogen also increases progesterone receptor (PR) expression in OL cultures [94], and progesterone, as described in our companion review promotes OLgenesis [1]. Combining estradiol with progesterone also enhances remyelination to an even greater extent and increases the number of immature and mature OLs [93]. Thus, administration of both progesterone and estradiol produces synergistic effects, more effectively restoring myelination and reducing inflammation [38,93]. Collectively, these findings emphasize the need to investigate the complex interactions between hormones in the context of disorders.

Estrogen replacement therapy may also play a role in protecting middle-aged women from adverse effects following menopause, including myelin abnormalities and impaired cognition [95–97]. Such protection may in part be due to estrogen's effects on OLs and myelination. Middle-aged (9-12 month old) female ovariectomized (OVX) rats receiving one month of E2 replacement therapy retained a higher volume of white matter myelin sheaths compared to OVX rats receiving placebo [96,98]. Myelin fiber length and diameter increased, which correlated with improved spatial learning in the OVX middle-aged female mice [96]. Thus, estrogen replacement therapy's benefits on cognitive decline may arise, in part via protection of white matter [99]. The mechanisms of estrogen's beneficial effects remain to be determined, and indeed, future work may determine if this protection occurs via OL survival and/or effects on OLgenesis.

2.2.2. Progestogens

The steroid hormone progesterone is commonly known for its role in the maintenance of pregnancy, yet it also has a wide range of functions in the body and throughout the CNS, including effects on OLgenesis [1]. Progesterone acts primarily on nuclear progesterone receptors (PRs) to stimulate OPC differentiation and upregulate MBP levels [100]. Progesterone can also act via membrane bound PRs (mPRs) and interestingly mPRs, though typically only found in neurons, are expressed in OLs following injury, suggesting a selective role for mPRs in injury recovery [101].

Implications for disorders:

Progesterone has a significant impact on remyelination, with important implications for demyelinating disorders and other injuries characterized by alterations in myelin in adults (for a recent review, see [73]. Progesterone's ability for myelin repair in the adult CNS extends across multiple injury models, including: SCI, LPC or cuprizone-induced demyelination, as well as animal models of MS, including EAE.

In SCI models, chronic treatments with progesterone enhance OPC proliferation, differentiation, and increase remyelination following injury [102–107]. In fact, OPC differentiation is arrested after SCI and is only reinstated following treatments with progesterone [104]. While a complete mechanism for this effect has not been determined, progesterone may exert indirect effects on OL differentiation through upregulation of Transforming Growth Factor-Beta 1(TGF-β1), a known OL differentiation factor [102]. In addition to effects on differentiation and remyelination, progesterone also improves survival of OPCs following injury, in part by reducing pro-inflammatory cytokines [108]. This effect requires a functional PR and is not observed in PR knock-out animals [108]. Lastly, progesterone-induced increases in mature OLs and MBP immunoreactivity are

associated with positive functional outcomes, such as improved gait, making progesterone a promising future avenue for treatment [107].

Similar to findings in SCI models, progesterone has protective and pro-remyelinating effects in LPC, cuprizone, and other toxin-induced demyelination models [109–111]. Progesterone not only enhances myelination of axons; it also increases the density of OPCs and mature OLs [109]. Progesterone acts to increase OPC proliferation, differentiation, and migration to the injury site via a mechanism involving the nuclear PRs [110]. Furthermore, a synthetic derivative of progesterone that selectively targets PR, nestorone, stimulates OPC proliferation, migration, and differentiation in cerebellar slice cultures treated with LPC, but at a much lower dose than natural progesterone [110]. Similar findings are observed *in vivo*, where progesterone and nestorone increase the density of OPCs and mature OLs, and enhance the formation of myelin proteins such as PLP and MBP [93,112]. Again, these effects were dependent on PR and were not observed in PR knock-out animals [112].

In inflammatory models of MS, such as the rodent EAE model, progesterone improvement of remyelination may occur through its beneficial influence on inflammation, reducing inflammatory cell infiltration, proinflammatory cytokines, and reactive microglia [113–116]. In MS, OPCs fail to differentiate into remyelinating OLs [117]. Progesterone, however, affects a transcription factor that contributes to OL differentiation, oligodendrocyte transcription factor 1 (Olig1), increasing its movement from the cytoplasm into the nucleus, thereby promoting OPC differentiation [118]. Functionally, treatment of EAE animals with progesterone improves clinical outcomes [113,115,119]. Together, these findings position progesterone as a strong candidate for future therapies in MS patients. Interestingly, MS patients express lower levels of the progesterone metabolite, allopregnanolone [39]. Reduced allopregnanolone may contribute to the impaired OPC differentiation observed in MS. However, whether reduced neurosteroid synthesis and metabolism contribute to disease pathology or are simply biomarkers remains unknown.

While progesterone has primarily been studied in the context of SCI and demyelinating disorders, it also has beneficial effects for other disorders associated with myelin loss, such as Alzheimer's disease and stroke [4,120,121]. For example, progesterone and allopregnanolone have protective effects in an animal model of Alzheimer's Disease, increasing not only neurogenesis, but also expression of 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase), a myelin associated enzyme that marks mature OLs [122,123]. Thus, progesterone may have protective effects across the lifespan. Furthermore, following stroke, progesterone promotes increased density of both OPCs and mature OLs [124]. Altogether, progesterone shows the same pro-OLgenesis effects in adult animals following injury as that observed in development [1]. Future work will undoubtedly continue to explore the mechanisms by which progesterone acts and to assess the functional impact of OLgenesis in these models.

2.2.3. Androgens

Androgens are a class of steroid hormones that includes testosterone (T, the primary circulating androgen in males), dihydrotestosterone (DHT, a metabolite of T and the most potent androgen), and several weakly acting hormones [125]. Androgens primarily act via a nuclear receptor, the androgen receptor (AR). While it remains unclear whether androgens act directly on OLs, androgen signaling through the AR promotes OLgenesis and subsequent myelination *in vivo*, though other *in vitro* work suggests that androgens may also moderately enhance OL cell death [1,126].

Implications for disorders:

Studies reporting androgen-induced OL cell death under physiological conditions are somewhat at odds with several studies demonstrating a protective effect of T in demyelinating disorders. Indeed, early studies suggested that in EAE models, castration induces clinical relapses and a greater influx of activated T-cells into the CNS, suggesting that male gonadal hormones are protective [127]. Moreover, administration of T prior to

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and concurrently with EAE induction results in reduced clinical scores in male and female mice, as well as increased expression of IL-10, an anti-inflammatory cytokine [128,129]. Administration of DHT, which cannot be aromatized to estrogens, yields similar improvements in clinical scores and neuroinflammatory markers [129,130]. Given that androgens are known modulators of immune function, it is possible that these benefits in the EAE model may be attributed to the suppression of neuroinflammation rather than direct effects on OLs and myelin [131].

Androgens can also enhance remyelination following toxin-induced demyelination. For example, 12 weeks of cuprizone administration results in long-lasting loss of OLs and myelin in the corpus callosum of both castrated male and ovariectomized female mice; however, administering T for 6 weeks following cuprizone withdrawal increases the number of OPCs, and restores mature OL numbers and MBP expression in both sexes, suggesting the T enhances OPC recruitment, differentiation, and remyelination [132]. This rescue is blocked by genetic knockout of AR function in neurons and macroglia ($AR^{Nestin\text{-}Cre}$ mice). Furthermore, this myelin-rescuing effect can be mimicked *in vitro* in cerebellar slice culture; applying T or DHT following LPC-induced demyelination restores myelination, an effect that is blocked by an AR antagonist. Together, these data suggest AR signaling has a direct role in CNS remyelination [132]. Similar results were found in a model of spinal cord demyelination induced by LPC injection [133]. Specifically, 3 days of T administered immediately following LPC injection increased myelination of the spinal cord. Notably, however, genetic knockout of CNS AR signaling did not completely block the effect of T in this model, suggesting that, at least in the spinal cord, T exerts some protective and/or remyelinating effects through non-AR signaling [133]. It was further demonstrated that T increases the number of proliferating OL lineage cells in the LPC-treated spinal cord *in vivo*, and that T increases the number of mature OLs in neonatally-derived mixed glial cultures following LPC treatment *in vitro* [133]. Overall, these studies suggest that T promotes remyelination by promoting OPC proliferation and differentiation and subsequent remyelination. Nonetheless, the exact mechanism of this rescue is unresolved. In particular, OL survival was not assessed in these experiments. In addition, it is unclear whether androgens act directly on OPCs and OLs, or indirectly through effects on surrounding cell types.

Although the mechanism of action remains somewhat unclear, the ability of androgens to protect against demyelination and enhance remyelination may ultimately have implications for disorders such as MS. Reports suggest that women are more susceptible to MS than men [12]; however, men may have a more aggressive progression of disease [134]. In addition, men tend to display a later onset of disease that coincides with age-related declines in T levels, and lower T levels are associated with greater disability scores and worse disease course in men with relapsing-remitting MS (RRMS) [135]. Androgens have, thus, emerged as a potential therapeutic target for MS. In a small preliminary clinical trial conducted in a cohort of 10 men with RRMS, T supplementation enhanced performance in an auditory processing task and attenuated brain atrophy [136]. However, overall disability scores and lesion volumes were unaffected. Subsequent follow-up and analysis of this same cohort revealed that T supplementation reduced, and perhaps even reversed, gray matter volume loss and promoted anti-inflammatory immune profiles [137,138]. Together with the animal literature, this may suggest that androgens inhibit neuroinflammation, which in turn attenuates tissue loss, but may have little effect on myelin lesions themselves. Understanding the direct and indirect effects of androgens on OLs will, therefore, be critical to the future of androgen therapy in demyelinating disorders. Larger, well-controlled clinical trials will enhance our understanding of androgens' modulation of OLgenesis in adulthood and their capacity to serve as therapeutic targets for demyelinating disorders. In sum, androgens offer a promising target to promote remyelination, but many questions remain surrounding the effects of androgens on OLgenesis and remyelination. Namely, it is unclear whether androgens promote OL survival, whether they modulate OLgenesis and remyelination outside of mouse models, and whether they act directly or indirectly on OLs.

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3. Amino Acid-Based Hormones (Peptides, Amines, Thyroid Hormones)

In this section, we discuss the role of amino acid-derived hormones and their receptors in OLgensis and myelin repair. These hormones can be genetically-encoded chains of two or more amino acids (peptides) or enzymatically altered compounds derived from single amino acids (amines and thyroid hormone). As we describe in our companion review, many of these hormones act to enhance OPC proliferation and/or OL survival through common signaling pathways [1].

3.1. Insulin-like Growth Factor 1 (IGF-1)

IGF-1 is a peptide that broadly contributes to cell growth, proliferation, differentiation, and survival. IGF-1 exerts its effects in part by binding the IGF-1 receptor (IGF1R), which is expressed in all CNS cell types, including OLs [139–142]. In a developmental context and under physiological conditions, IGF-1 promotes OLgenesis and increases the number of mature, myelinating OLs by promoting OPC and OL survival and enhancing NSC and OPC differentiation [1,139,143].

Implications for disorders:

The effects of IGF-1 on OL survival and differentiation may have important implications for adult demyelinating disorders. Specifically, IGF-1 exerts protective effects in several animal models of myelin damage. In alignment with the anti-apoptotic effects of IGF-1 under physiological conditions, administering IGF-1 or constitutively overexpressing IGF-1 prevents OL apoptosis and/or myelin loss induced by a host of demyelinating conditions, including cuprizone treatment, LPC treatment, undernourishment, and ischemia [144–147]. An IGF1R agonist has similar protective effects in an ischemia model [148]. Furthermore, in mixed glial cultures, IGF-1 attenuates apoptosis of mature OLs induced by the inflammatory cytokine TNF-α [149]. Notably, each of these studies administered IGF-1 immediately following myelin insult or utilized an animal model with constitutive overexpression of IGF-1.

IGF-1 has also been targeted as a potential treatment for demyelinating disorders such as MS. Interestingly, constitutive loss of IGF1R impairs OPC survival, proliferation, and subsequent OL remyelination after cuprizone-induced demyelination ([140]cite), again suggesting that IGF-1 plays an important role in OL survival. In the rodent EAE model of MS, 8 days or 10 days of IGF-1 administration improved clinical movement deficits and lesion numbers [150,151]. Despite these promising studies, however, other experiments call into question the efficacy of IGF-1 treatment for MS. For example, while a 14-day treatment with IGF-1 ameliorated lesion severity, this effect was transient, and IGF-1 treatment had no lasting effect on remyelination [152]. Furthermore, IGF-1 only conferred benefits when administered immediately following EAE induction; IGF-1 treatment that was begun well past clinical onset had no effects on disease severity and myelin lesions [152]. Similarly, viral-induced upregulation of IGF-1 begun 8 days after LPC-induced demyelination in the spinal cord had no effect on remyelination in aged rats [153]. Together, these results may suggest that IGF-1 is primarily protective against initial demyelination and OL apoptosis, and as a result, IGF-1 treatment is only effective when given immediately following myelin insult. Consistent with this, a pilot clinical trial in 7 MS patients with established disease onset found that treatment with recombinant human IGF-1 is ineffective [154]. Thus, despite the ability of IGF-1 to promote the survival of cells from the OL lineage and to enhance OLgenesis under physiological conditions, results from IGF-1-based treatments in demyelinating disorders are mixed. IGF-1 may serve as a preventative treatment that decreases initial disease burden but does not have persistent benefits. Clinical trials with MS patients early in disease onset and detailed studies of the *in vivo* mechanisms of IGF-1-induced OLgenesis and remyelination are needed. Special attention should be paid to the experimental time points of IGF-1 treatment to determine whether IGF-1 is a viable preventative and/or therapeutic target for demyelinating conditions.

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3.2. Insulin

Insulin is a metabolic hormone that classically regulates glucose homeostasis but also acts within the CNS in both a hormonal and paracrine fashion [155]. Insulin binds to the insulin receptor (IR), expression of which is detected in OLs [156], and can also bind to IGF1R, albeit with a lower affinity [157]. While less is known about insulin's IR-mediated effects on OLgenesis, insulin likely increases OPC survival and differentiation via mechanisms akin to those of IGF-1 [1].

Implications for disorders:

Despite insulin's ability to promote OL survival, treatment with insulin appears to be ineffective in demyelinating disorders. In both young and aged EAE animals, chronic treatment with IGF-1, but not insulin, ameliorates clinical severity scores [147]. Given that insulin requires considerably higher concentrations to promote OL survival compared to IGF-1 [158], this may suggest that insulin is not potent enough to protect against demyelinating insults.

Insulin's interactions with IR and IGF1R and its effects on OLgenesis may have implications for disorders that present with significant disruptions in insulin signaling, such as type 1 and type 2 diabetes. Indeed, peripheral demyelination is a common diabetes-induced complication, and insulin signaling may contribute to myelin production in Schwann cells ([159–161]. However, disrupted insulin signaling may also affect myelination in the CNS. In cell culture, the absence of insulin decreases nuclear Olig1 levels in OPCs, which is necessary for differentiation of OPCs into mature OLs (Gong et al., 2008), and insulin contributes to OL survival [163,164]. Furthermore, patients with adult diabetes may present with abnormalities in white matter content that correlate with cognitive function, suggesting a potential link between blood insulin and white matter structure [165–167]. In middle aged humans, both insulin resistance and insulin levels are associated with altered MRI-based estimates of myelin content [168]. However, in this study, there was region-related heterogeneity of these relationships; myelin content in the frontal and temporal lobes was positively correlated with insulin levels, while parieto-occipital myelin was negatively correlated with insulin levels. Such regional specificity has not been reported or thoroughly investigated in animal models of IGF1R upregulation. Future work could address this by investigating regional heterogeneity of the effects of insulin and IGF-1 signaling on brain myelination, as well as relating insulin action to myelination in animal models of obesity or diabetes. These data point to IGF-1 and insulin effects on OLgenesis and myelin changes as a potential mechanism underlying the cognitive and neurological sequelae of diabetes. Overall, more research is needed to determine whether insulin acts on IR or IGF1R to alter myelination in diabetic humans and animals.

3.3. Prolactin

Prolactin (PRL) is a peptide that is best known for promoting lactation but that also regulates diverse functions including OLgenesis [1]. While circulating PRL is produced by the anterior pituitary, PRL can also be produced locally in the brain [169–173]. Though effects of PRL have not been studied across the entire OL lineage, under physiological conditions, PRL increases OPC proliferation and differentiation, suggesting it overall promotes OLgenesis [174].

Implications for disorders:

PRL has garnered interest for its potential to act as a therapeutic candidate for demyelinating disorders such as MS. This interest began with early observations that female MS patients show fewer relapses during the third trimester of pregnancy, when PRL levels are high [34]. Furthermore, PRL plasma levels in female MS patients are positively correlated with white matter volume [175]. Given this relationship and the potential enhancement of OLgenesis by PRL in animal models [174], research has tested whether PRL aids remyelination after myelin damage. Indeed, pregnancy is protective

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against LPC-induced demyelination in the mouse spinal cord, with pregnant mice displaying decreased lesion size and increased numbers of proliferative immature OLs at the injury site [174]. Although the necessity of PRL signaling was not tested in this model, PRL injections into virgin mice were sufficient to mimic this protective effect [174]. While this suggests positive effects of PRL on OPC differentiation, the effects of PRL injections on OL survival were not tested. Moreover, these experiments were conducted in female mice; the effects of PRL on remyelination in male mice are not known.

While these results are promising, PRL has known pro-inflammatory effects that could complicate its use as a treatment in disorders such as MS and antagonize its remyelination benefits [173]. In fact, lymphocytes produce PRL, potentially serving as an autocrine signaling factor for these cells, and PRL levels are elevated in a mouse model of EAE [173,176,177]. Indeed, in the EAE model, PRL enhances lymphocyte proliferation in response to exogenous myelin proteins, and treating animals with PRL has no effect on disease severity after EAE induction [178]. These findings may indicate that treating inflammatory-induced myelin damage with PRL is not only ineffective, but also potentially harmful and pro-inflammatory. Consistent with this, PRLR knockout mice have a slight delay in EAE onset and eventually have full clinical severity [179]. However, coupling PRL with interferon-β ameliorates clinical scores, suggesting that PRL treatment may be beneficial when PRL's actions on immune cells are inhibited [178]. Overall, these studies paint a complicated picture of PRL's role in OLgenesis and remyelination after injury. Considerably more studies conducted both *in vitro* and *in vivo* will be necessary to parse PRL's separate actions on OLs and immune cells. Understanding the interaction of such effects will determine whether PRL improves or hinders disease severity and disease-related OLgenesis.

3.4. Melatonin

Melatonin is an indolamine neurohormone produced primarily by the pineal gland, and to a lesser extent, locally within the brain, that regulates circadian rhythms and exhibits anti-inflammatory actions [180–182]. Both of the melatonin receptors are expressed by OLs [183]. Though the mechanisms remain unclear, melatonin increases NSC differentiation towards an OL fate, increases OL maturation both *in vitro* and *in vivo*, and enhances OL survival by inhibiting expression of the apoptotic factor caspase-3 [1].

Implications for disorders:

Few studies have examined the molecular effects of melatonin on OLgenesis under physiological conditions; however, several have examined melatonin's protective effects under demyelinating conditions. Such conditions include ischemia [184,185], stroke [186], and EAE [187,188]. These studies largely showed melatonin treatment mitigates the loss of MBP+ fibers and mature OLs in regions such as the cingulum bundle, corpus callosum, and hippocampus [184–187]. In parallel with the amelioration of myelin loss were improvements in neurological disability scores [187,188]. In addition, 3 days of melatonin treatment rescued myelin density and partially restored the number of mature OLs in the cingulate and corpus callosum of neonatal rat pups subjected to uterine artery ligation [183]. These studies support the hypothesis that melatonin, acting either directly on OPCs and OLs, or indirectly via microglia and astrocytes, is protective against myelin damage. Notably, only one of these studies examined the effect of melatonin on OLgenesis post-injury and found that melatonin treatment increased OPC proliferation [184]. The role of melatonin on OL survival, OPC differentiation, and OL remyelination are only beginning to be explored. Melatonin administered in the final 7 days of cuprizone-induced demyelination in mice decreased markers of apoptosis in the corpus callosum; however, melatonin had no effect on remyelination [189]. This may suggest that melatonin's effects are largely pro-survival, rather than pro-remyelination. Alternatively, longer treatment and/or observation times may be needed to observe the beneficial effects of melatonin. Interestingly, one study has suggested that melatonin

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administration in an adolescent rat EAE model exacerbates neurological disability scores [190]. Whether melatonin's protective effects are age-specific remains unresolved.

Many of the studies noted here also investigated the effects of melatonin on inflammation. Consistent with melatonin's anti-inflammatory properties, melatonin treatment decreases pro-inflammatory cytokine levels in cuprizone-induced demyelination, EAE, and ischemia [184,186–188,191]. In addition, melatonin normalizes the numbers of reactive microglia and infiltrating lymphocytes in white matter regions and the spinal cord [186,187]. This may suggest that melatonin's anti-inflammatory properties mediate its protective effects on myelination; however, none of these studies tested a causal link between these effects.

In sum, melatonin may be a promising candidate for the prevention of demyelination and the amelioration of disease severity; however, the mechanism of melatonin action remains unclear. Melatonin consistently attenuates myelin loss and reduces levels of pro-inflammatory cytokines and microglial reactivity; however, no study has demonstrated a causal link between these two parallel effects.

3.5. Thyroid Hormones

Thyroid hormones (THs) are tyrosine-based hormones that act on almost every cell type in the body to regulate CNS development, including OLgenesis. [1,192–194]. These two hormones, the functionally active triiodothyronine (T3) and its precursor thyroxine (T4) are essential for the development and differentiation of OLs [195]. TH's pro-OLgenesis effects are mediated in part, through their action through the two forms of thyroid hormone receptors (TRs), TRα and TRβ, nuclear receptors that bind either as homodimers or heterodimers to thyroid response elements (TREs) in DNA to alter gene expression [196,197]. In addition, TRs dimerize with other nuclear receptors expressed in OLs [198], including retinoid X receptors (RXR), to exert effects on OLgenesis [199–201].

Implications for disorders:

It has long been known that TH deficiency, in both humans and other animals, leads to impairments in myelin during development [202–206] and that treatment with TH can reverse myelination deficits if given within a critical developmental window [207,208]. In addition, due to its pro-OLgenesis effects, THs have been studied as a potential treatment for demyelinating disorders [209]. In SCI in adult rodents, local delivery of T3 promotes new OL formation and increased myelination *in vivo* [210]. T3 also improves remyelination following cuprizone-induced demyelination [209,211–213]. Specifically, T3 increases numbers of both OLs and their precursors in the adult mouse brain [212]. Increases in TH-induced OPC differentiation following cuprizone injury are thought to be due to the TRβ, as TRβ was only faintly detected in demyelinated animals and receptor expression was upregulated following TH treatment [211]. TH may also improve re-myelination through upregulation of transcription factors like Krupple-Like Factor 9, a zinc finger transcription factor that aids in OPC differentiation (KLF9) [213].

In animal models of MS such as EAE, TH again aids in remyelination [214–218]. Similar to effects observed during development, TH treatment inhibits NSC proliferation and upregulates markers of OPCs and mature OLs [215–217]. This increase in OL differentiation may, in part, be due to transcriptional upregulation of Platelet-Derived Growth Factor Receptor Alpha (PDGFRα), another inductor of OL differentiation [217]. In addition to effects on OL differentiation and maturation, TH administration protects and repairs myelin sheaths, likely through enhancement of MBP protein expression [214,215,217]. Heterodimerization of TR with RXR may play a role in remyelination, as 9-cis-retinoic acid promotes remyelination in concert with THs both *in vitro*, in cerebellar slice cultures after demyelination by LPC, and *in vivo*, in aged EAE rats after demyelination [219]. Protective effects of TH are not limited to rodent models. TH-induced remyelination also occurs in non-human primates with EAE, and importantly, is associated with functional improvements on clinical scores [218]. TH's pro-remyelination effects may also be due to modulation of the immune system and

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immune factors such as inflammatory cytokines [220]. For example, T3 treatment reduces the number of pro-inflammatory IL-17+ T cells [221]. The interaction of THs and inflammatory markers will be an important area for future study. In fact, inflammation may reduce TH levels and that reduction in TH may play a causal role in MS pathology [222]. Overall, TH appears to be a promising avenue for treating demyelinating disorders. Clinical trials have recently begun testing the safety and efficacy of TH treatment for MS [223].

4. Future Directions

Broadly, hormonal actions on OLgenesis represent an underexplored therapeutic avenue for myelin repair. Yet, as we have noted throughout this review, there are many unanswered questions. For example, while many studies have shown that hormones have neuroprotective and pro-remyelination effects in animal models of white matter damage, their mechanisms of action remain largely unclear. Understanding these mechanisms will be crucial for designing therapeutics that target specifically OLgenesis and remyelination and minimize off-target effects in the CNS. In addition, many of these hormones both improve myelin loss and reduce inflammation. Thus, it remains to be determined if hormones act directly on the OL lineage to enhance remyelination or indirectly through interactions with the immune system and other factors.

In addition, few studies have addressed the complex interactions amongst the hormones themselves. For example, estrogen induces upregulation of progesterone receptors, and treatments with both estrogen and progesterone combined were more effective in restoring myelination [38,93,94]. In addition, PRL ameliorates disease severity in EAE, but only when its modulation of immune cells is dampened [178]. Future work could continue to elucidate such pleiotropic effects in order to design combinatorial treatments for demyelinating disorders.

Further, we have little understanding of how hormones might affect OLgenesis and myelin repair based on age. Indeed, the actions of several of the hormones discussed here change over the course of development and adulthood [1]. Thus, the effectiveness of hormonal strategies may depend on an individual's age and their circulating levels of hormones, which differ in children, adolescents, and adults. Future studies *in vivo* should therefore test hormonal effects on OLgenesis and remyelination across the lifespan. Similarly, there is a dearth of work testing hormonal effects on myelination in an aging context. Aging alone leads to white matter loss, and the effect is exacerbated in patients with AD [4,224–226]. While a handful of studies have demonstrated pro-remyelinating effects of hormones in an AD model [123,227], their mechanisms of action remain unclear and many of the classical hormones we described here have yet to be tested in AD models. Lastly, while we have detailed the effects of a range of different hormones on OLgenesis and remyelination in the context of disease, there are many more hormones that might regulate OLgenesis, including classical and non-classical hormones such as gut hormones, epinephrine, and norepinephrine. For example, in the mouse EAE model, the secretin hormone vasoactive intestinal peptide (VIP) ameliorates disease severity, prevents demyelination, and prevents the death of mature OLs in the spinal cord [228]. Overall, the field has enormous potential, with numerous future directions.

5. Conclusions

Hormones across many classes exert protective and remyelinating effects on disorders characterized by myelin loss. Many of these hormones, including IGF-1, thyroid hormones, and steroid hormones, act through both direct actions on OLs, and indirect mechanisms, such as through immunomodulation (Figure 1). Better understanding of hormonal mechanisms and the circumstances under which they act, such as age and disease onset, will allow for more targeted therapeutics for disorders that lead to OL damage and demyelination.

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Appendix - List of Abbreviations

AD
: Alzheimer's Disease

AKT
: Phosphatidylinositol 3-kinase

AMPA
: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AR
: Androgen Receptor (nuclear)

CNPase
: 2',3'-Cyclic-nucleotide 3'-phosphodiesterase

CNS
: Central Nervous System

Cort
: Corticosterone

Dex
: Dexamethasone

DHT
: Dihydrotestosterone

E2
: 17-β estradiol

EAE
: Experimental Autoimmune Encephalomyelitis

ER
: Estrogen Receptor (nuclear)

GC
: Glucocorticoid

GM
: Grey matter

GR
: Glucocorticoid Receptor (nuclear)

HPA
: Hypothalamic-Pituitary-Adrenal

IGF-1
: Insulin-Like Growth Factor-1

IGF1R
: Insulin-Like Growth Factor-1 Receptor

IR
: Insulin Receptor

KLF9
: Krupple-Like Factor 9

LPC
: Lysophosphatidylcholine

MBP
: Myelin Basic Protein

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MP
: Methylprednisolone

mPR
: membrane bound PRs

MS
: Multiple Sclerosis

mTOR
: Mammalian Target of Rapamycin

NPC
: Neural Progenitor Cell

NSC
: Neural Stem Cell

OL
: Oligodendrocyte

OLgenesis
: Oligodendrogenesis

Olig1
: Oligodendrocyte transcription factor 1

OPC
: Oligodendrocyte Precursor Cell

OVX
: ovariectomized

PDGFRα
: Platelet-Derived Growth Factor Receptor Alpha

PI3K
: Phosphatidylinositol 3-kinase

PRL
: Prolactin

PR
: Progesterone Receptor (nuclear)

PTSD
: Post-Traumatic Stress Disorder

RRMS
: Relapsing-Remitting MS

RXR
: Retinoid-X Receptors

SCI
: Spinal Cord Injury

T
: Testosterone

T3
: Triiodothyronine

T4
: Thyroxine

TGF-β1
: Transforming Growth Factor Beta 1

TH
: Thyroid Hormone

TR
: Thyroid Hormone Receptor (nuclear)

TRE
: Thyroid Response Element

VIPqq

Vasoactive Intestinal Peptide

WM White matter

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