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Review

Hormonal regulation of oligodendrogenesis I: effects across the lifespan

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Abstract: The brain's capacity to respond to changing environments via hormonal signaling is critical to fine-tuned function. An emerging body of literature highlights a role for myelin plasticity as a prominent type of experience-dependent plasticity in the adult brain. Myelin plasticity is driven by oligodendrocytes (OLs) and their precursor cells (OPCs). OPC differentiation regulates the trajectory of myelin production throughout development, and importantly, OPCs maintain the ability to proliferate and generate new OLs throughout adulthood. The process of oligodendrogenesis (OLgenesis), the creation of new OLs, can be dramatically influenced during early development and in adulthood by internal and environmental conditions such as hormones. Here, we review the current literature describing hormonal regulation of OLgenesis within physiological conditions, focusing on several classes of hormones: steroid, peptide, and thyroid hormones. We discuss hormonal regulation at each stage of OLgenesis and describe mechanisms of action, where known. Overall, the majority of hormones enhance OLgenesis, increasing OPC differentiation and inducing maturation and myelin production in OLs. The mechanisms underlying these processes vary for each hormone but may ultimately converge upon common signaling pathways, mediated by specific receptors expressed across the OL lineage. However, not all of the mechanisms have been fully elucidated, and here, we note the remaining gaps in the literature, including the complex interactions between hormonal systems and with the immune system. In the companion manuscript in this issue [1], we discuss the implications of hormonal regulation of OLgenesis for neurological and psychiatric disorders characterized by white matter loss. Ultimately, a better understanding of the fundamental mechanisms of hormonal regulation of OLgenesis across the entire lifespan, especially *in vivo*, will progress both basic and translational research.

Keywords: oligodendrogenesis, hormones, mechanisms, steroids, peptides

1. Introduction

The human brain is able to undergo dramatic plasticity throughout life in response to both internal and external signals. Classically, neurogenesis, or the generation of new neurons, is regarded as a major form of plasticity [2]. However, the generation of new glia, or gliogenesis, is a lesser explored yet equally important avenue for investigation. Specifically, oligodendrogenesis (OLgenesis), the creation of new oligodendrocytes (OLs), has recently emerged as a novel mechanism for experience-dependent plasticity in the developing and adult brain [3,4].

OLs are a class of glial cells in the central nervous system that produce myelin, a lipid rich membrane that enwraps and insulates axons. Myelin is canonically known for its role in enhancing the speed of neuronal transmission [5]. However, OLs and their associated

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myelin have also been found to regulate plasticity. Specifically, myelin proteins inhibit axonal sprouting and are thought to close critical periods and crystallize circuits [6,7]. In the adult brain, myelin can undergo considerable reorganization in response to neural activity; this experience-dependent myelination ultimately contributes to motor function, spatial and motor learning, social behavior, and emotional affect [3,8–12].

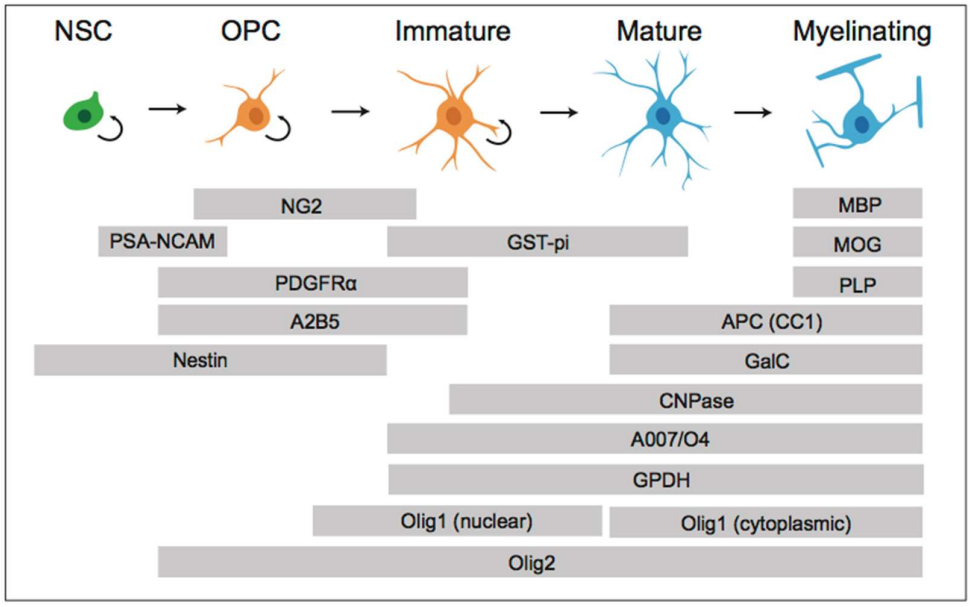

Figure 1. Cellular markers across the OL lineage.

Myelin plasticity in the central nervous system is driven in large part by OLgenesis. OLgenesis occurs heavily during early development yet also continues throughout adult life. As with neurons, OLs are originally derived from multipotent neural stem cells (NSCs) that maintain the capacity for self-renewal and can differentiate to adopt a neural or glial fate. These processes are tightly regulated by numerous factors, and the progression from NSC to mature OL can be tracked by the expression of characteristic cellular markers (Figure 1). For example, at the earliest stages, a subset of Nestin+ NSCs can develop into oligodendrocyte pre-precursors (OPPs), proliferative cells that default towards a glial cell fate and express the polysialylated adhesion molecule PSA-NCAM. A subset of OPPs become dedicated oligodendrocyte precursor cells (OPCs), precursors committed to the OL lineage; OPCs express a characteristic surface proteoglycan, neuron-glial antigen 2 (NG2), which allows them to be labeled and tracked in situ [13]. Other markers such as platelet derived growth factor receptor alpha (PDGFR-α) and the cell surface ganglioside A2B5 also are observed in OPCs and pre-oligodendrocytes [14]. A number of transcription factors, such as oligodendrocyte transcription factor 1 (Olig1), drive OPCs to differentiate into pre-OLs and immature OLs, and along with additional markers such as O4, Olig1 labels cells that have adopted an OL fate [14]. In contrast to Olig1, oligodendrocyte transcription factor 2 (Olig2) is expressed throughout the entire OL lineage [14]. At the final stages of maturation, OLs start to produce myelin and express markers unique to myelination, including myelin basic protein (MBP) and proteolipid protein (PLP) [14]. These markers are consistent across both developmental and adult OLgenesis, and their detection is crucial for understanding the stages and regulation of OLgenesis. It should be noted, however, that the exact delineations of the stages of OLgenesis, e.g. when a cell is considered “immature” vs. “mature,” varies considerably across the literature, and the majority of studies only utilize one marker to define cell stage. A growing number of studies suggest that adult neural and glial precursors are heterogeneous populations, and many of the markers noted above can be expressed by cell types not of the OL lineage; for

example, PSA-NCAM is also found in neurons and NG2 in pericytes [15,16]. Thus, future work should utilize multiple cellular markers or additional methods in order to be confident of cellular stage.

During mammalian development, OPCs originate from the ventricular germinal zones of the embryonic neural tube [17]. OPCs proliferate and migrate throughout the developing brain, and ultimately differentiate into mature, myelinating OLs. Although the production of myelinating OLs peaks in the first few weeks of life, there are regional differences in myelin maturation. For example, sensory areas myelinate earlier in life, while regions such as the prefrontal cortex extend myelination through adolescence and early adulthood [18]. Importantly, not all OPCs differentiate into OLs; a population of progenitors persist throughout the lifespan and retain the ability to proliferate and differentiate into OLs [19]. These OPCs are sensitive to neural signaling and respond to neural activity by proliferating and differentiating [20]. In addition, OPCs mobilize and differentiate into OLs in response to injury and demyelination, allowing for new myelination and repair [21,22]. Thus, OLgenesis is a lifelong process in the central nervous system (CNS), with ultimate implications for development, circuit function, behavior, and various brain insults. Understanding how adult OPCs are regulated could lead to promising therapeutic avenues for demyelinating disorders such as multiple sclerosis (MS).

OLgenesis is a complex process, and the mechanisms that control OLgenesis are under active investigation. OPCs and OLs are sensitive to numerous factors, including growth factors and a wide array of hormones [23–26]. Hormones, at their broadest definition, consist of a signaling molecule synthesized within an organism that acts upon an effector via a selective receptor. Hormones communicate to distant organs without the need for direct, neural innervation, and they have wide-reaching effects on an organism, from cognitive responses to stress to homeostatic regulation of blood ion concentration [27]. The production of hormones also changes across development and at critical stages of life, including during puberty and whilst pregnant. Various hormones, including estrogens and stress hormones, alter neurogenesis in developing and adult mammals [28–30]. However, the role of hormones in gliogenesis, and in particular, OLgenesis, is less understood.

In this review, we will explore how hormonal factors influence proliferation, differentiation, and survival across the OL lineage. We will restrict our discussion to the "classic" endocrine signaling molecules, which are typically released from a gland into circulation to act upon distant tissues. However, several of the hormones discussed can also be produced by tissues in the CNS, thus acting in a paracrine fashion. This review will describe the effects of several major classes of hormones on OLgenesis, including steroid hormones (glucocorticoids and sex hormones) and amino-acid based hormones (peptides, amines, and thyroid hormones). For each hormone, we will describe effects across the OL lineage in both development and adulthood, noting mechanisms where they are known. In a second, companion review [1], we discuss the implications of hormonal regulation of OLgenesis for disorders characterized by alterations in OLgenesis. We end with a discussion of future directions and additional considerations.

2. Steroid Hormones

Steroid hormones are hydrophobic molecules synthesized from cholesterol that consist of three cyclohexanes and one cyclopentane with alternating enol and ketone groups [31]. 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. Stress hormones such as glucocorticoids, and sex hormones such as estrogen, progesterone, and testosterone, impact neurogenesis and gliogenesis in the CNS, as well as OL survival and remyelination in MS and other myelin related diseases [1,26,32,33]. As we will discuss below, steroid hormones influence OL development and myelination in both development and adulthood. In particular, cells across the OL lineage express the classical nuclear receptors of each steroid hormone, as well as additional membrane receptors. Through both

genomic and non-genomic mechanisms then, steroids act to increase OPC differentiation and enhance maturation/myelination of OLs.

2.1. Glucocorticoids

Glucocorticoids (GCs) are the primary stress hormones for almost all animals. This family includes endogenous cortisol (the primary GC for humans) and corticosterone (Cort; the primary GC for rodents), as well as synthetic hormones such as dexamethasone (Dex). GCs are released in a circadian manner, in response to physiological cues, and under stressful conditions [34]. They are the end product of the hypothalamic-pituitary-adrenal (HPA) axis, which starts in the hypothalamus and ends with the release of GCs from the adrenal cortex into the bloodstream [35,36]. As they are highly hydrophobic, GCs bind carrier proteins in the blood such as transcortin, also known as corticosteroid-binding globulin, in order to be transported [37].

GCs can bind to two receptors: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs), both of which are typically located in the cytoplasm [38]. When activated by ligand binding, the receptor-ligand complex translocates to the nucleus and induces changes in gene expression. The activation of these receptors produces effects all across the body, leading to the mobilization of energy substrates and the suppression of inflammation, among other functions [34]. GRs are also found in all cell types in the CNS [34]. In particular, GRs, and to a lesser degree MRs, have been identified in both immature and mature OLs [39–42]. The identification of GRs on OLs provides a direct mechanism by which stress hormones may alter OL development and myelination.

Effects on developmental oligodendrogenesis

GCs play an important and complex role in early OL cell development; while GCs can increase OL differentiation and maturation, their effects may depend on both timing and dosage. Several seminal studies found that postnatal adrenalectomy profoundly changes myelination in the developing brain [43,44], providing an initial indication that GCs may be involved in OL development and myelination. Some of the first evidence from *in vitro* studies suggested that GCs promote differentiation and survival of cells along the OL lineage. In mixed glial cell cultures generated from one week old rat pups, hydrocortisone not only enhanced survival of all glial cells, it also increased the ratio of OLs relative to other glial cell types [45]. In subsequent studies, an increase in the number of OPCs was also observed following Cort or Dex application to OPC enriched cultures (90% A2B5+), and GCs protected against inflammatory cytokine-induced cell death [46]. Yet, *in vivo*, administering Dex to neonatal rats for five days reduced the number of OPC (O4+) cells in the corpus callosum, and induced morphological changes associated with cell death [47]. Thus, GC effects on survival may differ *in vivo* or when levels of GCs exceed the physiological range.

GCs act to regulate the timing of OPC differentiation into OLs. In cultured OPCs purified from postnatal day (p) 8 rat brains, when in the presence of mitogens, GCs induced slowing of proliferation and increased OL differentiation from OPCs [48]. However, such stimulatory effects of GCs on OL differentiation are not always observed. For example, in OLN-93, an oligodendroglial cell line derived from p1 rats, Dex inhibited expression of 2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase), a marker of OL differentiation [49]. Differences in GC effects on differentiation may be dependent on developmental stage. In a study with cells cultured from embryonic rats, 15 days of Dex treatment increased the OL markers CNPase and MBP, while 25 days of Dex treatment inhibited these same markers [50]. It is unclear however whether this reduction of OL markers was due to the prolonged exposure to Dex or whether this effect was dependent on cellular developmental age. Further, this study utilized aggregated cell cultures containing both neurons and glia and thus, interactions between cell types cannot be ruled out.

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GCs may also affect OL maturation and myelogenesis in early development. Hydrocortisone treatment of primary cell cultures derived from newborn rat cortices increased transcripts and protein for three myelin markers: glycerol phosphate dehydrogenase (GPDH), a general marker of OLs, as well as MBP and PLP, proteins associated with mature OLs and the myelin sheath [51,52]. These effects of hydrocortisone were only observed when treating cells that had been in culture for at least nine days [52]. Future studies should therefore test whether these effects are age dependent by directly comparing OL cultures derived from neonatal animals with cultures derived from animals later in development.

Importantly, many of the studies described above used mixed glial cultures, and therefore, observed effects on OLgenesis could occur indirectly via GC-induced alterations in astrocytes or microglia. Indeed, a more recent study treated purified OPC and OL cultures derived from neonatal rats with Dex and found Dex had no effect on OLgenesis, and altered few gene transcripts [53]. In contrast, Dex led to widespread transcriptional changes in microglia and astrocyte cultures [53]. Thus, culture purity is an important consideration for future *in vitro* studies, and it remains unclear how interactions with other glial cells might affect OLgenesis.

Effects on adult oligodendrogenesis

GCs can also have an effect on OL differentiation, proliferation, and maturation in the adult brain. In line with observations in the developing brain, GCs inhibit OPC proliferation in adults. For example, in adult adrenalectomized rats, prolonged GC exposure (15 days of 10mg/kg) inhibits OPC proliferation, leading to fewer NG2+ cells in white and grey matter across the forebrain, including in much of the hippocampus [54]. A second study also found that one week of daily Cort injections (40mg/kg) led to reduced proliferation of Bromodeoxyuridine (BrdU)+/NG2+ OPCs in the adult rat hippocampus in the molecular layer and hilus regions, but not in the granule cell layer [55]. Further, 15 days of chronic unpredictable stress decreased the number of BrdU+ OPCs across the cerebral cortex of the adult rat [56]; this effect only appeared 3 weeks following stress exposure, and while overall numbers were reduced, the percentage of BrdU+/NG2+ cells was not changed [56]. It is worth noting that results from these studies are unable to piece apart whether stress and GCs have an effect on OPC survival or whether reduced numbers are due to increased OPC differentiation into mature OLs.

While these studies identified fewer OPCs in the hippocampus following GC administration, others have found that stress exposure increases OL markers such as GPDH in the adult hippocampus [57,58]. GPDH is an enzyme that is unique to OLs in the rodent brain and is known to be upregulated by GCs [59,60]. A study by our own lab also found that 7 days of either immobilization stress or Cort injections increased OLgenesis in the dentate gyrus of the adult rat hippocampus [61]. Specifically, stress and Cort decreased neurogenesis and increased OLgenesis, indicated by a greater percentage of BrdU+ cells co-labeled with MBP. In addition, in a tamoxifen-inducible Nestin-CreER transgenic mouse line with NSCs fluorescently identifiable by Yellow Fluorescent Protein (YFP), we found that Cort induces OLgenesis in the hippocampus, with a greater percentage of YFP+ cells co-labeled with GST-pi, a marker of immature to mature OLs. Further, exposure of cultured NSCs to Cort increased the pro-OL transcription factors Olig1 and Olig2 and the percentage of MBP+ cells. These effects were found to be dependent on GR signaling; blocking GRs with a dominant negative viral vector led to lower numbers of OLs and reduced pro-OL factors compared to controls [61].

Taken together, a complex picture emerges for GC effects, including decreases in OPC proliferation and increases in OLs. These reported studies utilized different stress timelines and analyzed different markers along the OL lineage. It is plausible that stress exposure, and/or stress hormones such as Cort, may reduce the number of dividing OPCs and instead push OPCs to differentiate into immature or mature OLs. Future studies should examine OPCs and OLs within the same study to test this hypothesis.

GCs also have an impact on adult OL maturation and myelin morphology. In a study by Miyata et al. (2011), daily water immersion and restraint stress for three weeks increased plasma Cort levels and induced morphological changes in OLs in the corpus callosum, resulting in greater OL arborization compared to control animals. This was replicated *in vitro* via administration of Dex for 2 days in OL cell cultures. These stress-induced morphological changes are dependent on serum glucocorticoid regulated kinase 1 (SGK1) and endogenous Ɲ-myc downstream-regulated gene 1 (NDRG1) signaling. Stress exposure leads to increased SGK1 phosphorylation, and subsequent increases in NDRG1 phosphorylation; together SGK1 and NDRG1 upregulate the expression of adhesion molecules in OLs, specifically N-cadherin, and alpha- and beta-catenin, molecules involved in the stabilization of adherens junctions. While many other adhesion molecules expressed in OLs have been shown to aid in OL-axon signaling, promoting myelination [62], the functional role for these particular adhesion molecules in OLs remains unknown. In OLs cultures derived from neonatal rats, overexpression of SGK1 and NDRG1 was sufficient to replicate the effects of Dex and stress, confirming a role for this pathway in stress-induced alterations of OL morphology [63]. A subsequent study found that exposure to acute stress also led to increased SGK1 expression in mature, MBP+ OLs. This effect was absent in adrenalectomized mice and restored with Cort injections, indicating Cort is necessary for this effect [64]. Cort-induced changes in SGK1 expression were observed in white matter OLs, but not in grey matter OLs [64]. Future work could aim to determine why only grey matter OLs were affected. In addition, further work is needed to identify both direct and indirect mechanisms by which GCs affect OLgenesis. For example, GCs can also exert indirect effects on OLgenesis through their interaction with other hormones. In particular, high levels of GCs reduce thyroid functioning, leading to less conversion of thyroxine (T4) into the active triiodothyronine (T3), and as will be described in a later section, thyroid hormones also tend to have pro-OLgenesis effects [65,66]. Thus, high levels of GCs could in fact inhibit OLgenesis through these indirect interactions with other hormonal systems. *In vivo* studies will be necessary to explore such interactions and additional mechanisms of GC action.

2.2. Sex Hormones

Sex hormones, including Estrogens, Progestogens, and Androgens, all modulate OLgenesis and myelogenesis [26,67]. Interestingly, males and females display regional differences in white matter density [68,69]. Sex hormones might account for some of these sex-specific patterns of myelination.

2.2.1. Estrogen

Estrogen, the major female sex hormone, is produced primarily by the ovaries. Estrogen has many physiological functions for both male and female animals, including promotion of sexual maturation. Estrogen receptors (ERs) are found in many different cell types, including in OLs [70–73]. There are three major classes of endogenous estrogens: estrone, estradiol, and estriol. Of these, 17-β estradiol (E2) is considered to be the most potent and the most prevalent [74]. Interestingly, however, an optical isomer of E2, 17-α estradiol, is found at higher levels in the brain and can be produced in both sexes following gonadectomy [75]. While produced at higher levels in females, males also produce estrogen [76–78]. Specifically, tissues that contain aromatase, including in extragonadal sites, convert testosterone to E2 [79–81].

Estrogen primarily acts at two intracellular receptors, ERα and ERβ, both members of the nuclear receptor family. While both isomers of estradiol are able to bind to these ERs, ERα and ERβ differ in their localization in both the body and within the CNS [82,83]. In addition to intracellular ERs, estrogen can activate membrane bound receptors such as the G-protein coupled receptor, GPR30, which produce more rapid physiological

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responses [84–86]. Binding of GPR30 is estrogen selective; other hormones, including progesterone, cortisol, and testosterone, are not able to bind to GPR30 [87,88]. Collectively, activation of these receptors leads to the many downstream effects of estrogens.

Importantly, NSCs, OPCs, and mature OLs express all three forms of estrogen receptors: ERα, ERβ, and GPR30 [70–73,89–92]. Interestingly, in addition to being found in the nuclei, ERα and ERβ can also be localized in the membrane and cytosol of OLs, and the relative expression and localization of these receptors may change along the OL lineage [70,73,90]. For example, NSCs display higher expression of ERβ relative to ERα [92,93]. Localization of ERs may also differ based on OL maturity. For example, one group identified ERα localized primarily in the nucleus and ERβ primarily in the cytoplasm of OLs [73]. In contrast, others showed ERα expression in the cell membrane and perikaryon in addition to the nucleus, while ERβ was located mainly in the nucleus and only to a lesser extent along the membrane [71]. These discrepancies may arise from differences in the age or maturity of the cultured cells. For example, while OL cultures express both ERα and ERβ in the cytosol and nucleus, nuclear compartmentalization of both ERs increases as cells mature [90]. Interestingly, the relative density of ERs in OLs also differs based on sex. Levels of ERα in mature OLs are eightfold higher in females than males [90], indicating that estrogens may differentially affect males and females in part due to differences in ER expression. Regardless of localization or relative expression, activation of these receptors leads to changes in differentiation, proliferation, and maturation across OL development.

Effects on oligodendrogenesis

Broadly, estrogen regulates proliferation and differentiation across the OL lineage, beginning with NSCs. Specifically, E2 promotes NSC proliferation and differentiation. Notably, E2-induced proliferation is dependent on activation of nuclear ERs, while E2-induced differentiation is dependent on membrane-associated ERs [94]. Estrogen's effects on NSCs may also depend on cell culture conditions and interactions with other factors. For example, E2 prompts stem cells to differentiate into OL progenitors only when there are low levels of mitogens or other differentiation factors [92]. Under conditions where mitogens are present, and when there is physiologically appropriate dosing of E2, NSC differentiation is instead biased towards neuronal, rather than glial cell fates [89]. Age is also a factor, as E2 only increases the ratio of neurons to glia in embryonic NSCs, not in adult NSCs [93].

While the above studies did not explicitly test the relative contributions of ERα and ERβ in E2-mediated effects, others have focused on the specific roles of particular ER receptors. ERβ ligands inhibit proliferation of embryonic stem cells, and ERβ knock-out mice display enhanced OLgenesis [95], suggesting that activation of ERβ in particular may promote stem cell differentiation into neurons and prevent precocious OLgenesis. Little is known about the specific effects of ERα binding on NSC development. Indeed, activation of these different receptors may lead to diverging effects on OLgenesis and requires future investigation.

Like their neural stem cell counterparts, OPCs are also affected by estrogens. E2 delays the exit of OPCs from the cell cycle in a dose-dependent manner in response to mitogen withdrawal [91]. This allows OPCs to undergo additional rounds of cell division, and ultimately, can be interpreted as an estrogen-induced increase in OPC proliferation. In the presence of mitogens however, E2 does not affect OPC proliferation [90]. In addition to effects on proliferation, E2 can also enhance OPC differentiation and maturation, leading to thicker branching in the subsequent OLs [91]. In one study, tamoxifen, an ERα selective agonist, mimicked the E2 effect on proliferation, but not its effect on branching [91]. This indicates that estrogen-induced changes in OPC proliferation might be mediated by ERα while changes in cell morphology and maturation are instead mediated by ERβ. Interestingly, though, in a separate study, tamoxifen promoted OPC differentiation into OLs, stimulating progenitors to become mature OLs, suggesting ERα may indeed play a role in OPC differentiation. This effect was abolished in the presence of a pan-ER antagonist [96].

Similarly, diosgenin, a steroid precursor, promoted OPC differentiation into mature OLs through an ER-dependent mechanism; differentiation was blocked by a pan-ER antagonist, but not by either GC or progesterone receptor antagonists [97]. Estrogen-induced increases in OPC differentiation may also occur through more rapid activation of a Phosphatidylinositol 3-kinase (PI3K)/Protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway [98]. This pathway has been shown to be required for OPC differentiation into immature OLs [99,100]. Overall, through both genomic and nongenomic mechanisms, estrogens appear to stimulate OPC differentiation.

Similar to findings in OPCs, estrogens can also stimulate differentiation and maturation of immature and mature OLs, respectively [73,101,102]. Incubation of OLs with E2 increases cell branching and increases the number of cells with a snowflake shape, a stage in OL development that typically precedes formation of myelin sheaths [73]. In mature and myelinating OLs, estrogen also mediates remodeling of the cytoskeleton, acting via membrane-bound ERs. Notably, E2 and 17-α estradiol have opposing effects; while E2 induces a loss in microtubules and inactivates actin filaments, 17-α estradiol increases the percent of cells with actin filaments, indicating stabilization of the cytoskeleton [102]. This remodeling in mature OLs is important for functions such as OL extension and axon wrapping, which is relevant not only in a developmental context, but also across the lifespan. Future work should aim to explore these different pathways and how activation of different membrane ERs and nuclear ERs lead to changes in OL maturation.

2.2.2. Progesterone

The steroid hormone progesterone is part of a larger family of progestogens and is an important intermediate for other neurosteroids, including androgens and corticosteroids [103–105]. Though progesterone is commonly known for its role in the maintenance of pregnancy, it also has a wide range of functions in the body and throughout the CNS, including effects on sleep regulation and immune function [105]. For females, the corpus luteum in the ovaries is the major site of progesterone production. However, progesterone is also produced in the adrenal glands, in the placenta during pregnancy, and importantly, in the CNS of both females and males after birth and into adulthood [106]. Like all steroid hormones, progesterone is synthesized from cholesterol, which is then converted to the progesterone precursor, pregnenolone. The enzyme 3-β hydroxysteroid dehydrogenase (HSD) converts pregnenolone into its primary form, progesterone. Progesterone can also be metabolized by 5-α reductase to dihydroprogesterone (DHP), which is then metabolized further by 3-α HSD to allopregnanolone [107]. These metabolites have additional functions throughout the CNS, as will be described below.

Progesterone acts on two primary receptor classes: classical nuclear receptors and membrane-associated receptors, leading to genomic and non-genomic downstream effects, respectively. There are two forms of nuclear progesterone receptors (PRs): PRα and PRβ. Anatomically, these receptors are localized throughout the brain and spinal cord [108]. Functionally, PRβ is a more potent transcriptional activator, while PRα is primarily a transcriptional repressor [109,110]. Progesterone can also act on two forms of membrane-associated receptors to drive rapid, non-genomic effects: a 7 transmembrane domain membrane progesterone receptor (mPR) and membrane-associated progesterone receptor membrane component 1 (PGRMC1), which was previously referred to as 25-Dx [108]. Together, progesterone acts at these receptors to produce downstream actions in both the periphery and in the CNS.

Nuclear PRs have been identified in glial cells, and in particular, in OLs in both the brain and spinal cord [101,111,112]. Interestingly, PR expression increases with the addition of estrogen to primary glial cell cultures, suggesting PR expression can be regulated by other sex hormones [101,111]. Membrane-bound PRs have also been identified in the spinal cord [113]. In the brain, however, mPRs are typically only found in neurons and are only expressed in OLs following injury, suggesting a selective role for mPRs in injury

recovery [114]. Few have described how PR expression changes across the OL lineage. This will be an interesting area for further research and will provide insight into the mechanisms involved in progesterone's effects on OLs.

Interestingly, OLs not only express PRs, but they also directly synthesize progesterone and its precursor, pregnenolone. Synthesis of pregnenolone was first observed in glial cultures containing 60% OLs and occurred at the same time as OL differentiation [115]. Enzymes for progesterone synthesis have since been detected in OL cultures, and coincides with differentiation of bipotential oligodendrocyte-type 2 astrocyte progenitor cells (O-2A, now commonly referred to as OPCs) [116]. Later work confirmed that OPCs, and to a lesser extent, mature OLs, express mRNA of 3-β HSD, the key steroidogenic enzyme that converts pregnenolone to progesterone [117,118]. OLs and their precursors also contain enzymes for progesterone metabolism [118–120]. In contrast to 3-β HSD, the metabolism enzyme 5-α reductase is expressed five-fold higher in mature OLs relative to progenitors [118]. The enzyme 3-α HSD, which converts 5-α DHP to allopregnanolone, has also been observed in early progenitor cells, indicating a dissociation in the timing and pathways of progesterone metabolism in the OL lineage. The expression of PRs and the synthesis of progesterone and its metabolites across the OL lineage suggest that OLs may respond to progestogens in both an endocrine and autocrine fashion to regulate OLgenesis.

Effects on oligodendrogenesis

In general, progesterone and its metabolites stimulate OL proliferation, differentiation, and maturation across all stages of development [121]. At the NSC and OPP stage (PSA-NCAM+), progesterone stimulates cell proliferation. This effect is primarily mediated by conversion of progesterone to its metabolite, allopregnanolone, as blocking this enzymatic conversion inhibits progesterone's effect [119]. Allopregnanolone has also been shown to directly induce proliferation in both human and rat NSC cultures isolated from early in development [119,122,123]. These mitogenic effects are mediated by allopregnanolone acting as a positive allosteric modulator of GABA-A receptors; this in turn activates voltage-gated L-type calcium channels and drives cAMP response element-binding protein (CREB) signaling [119,122,123]. While allopregnanolone largely stimulates progenitor proliferation, its effects follow a bell-shaped curve, with high levels inhibiting proliferation [119,123]. Thus, use of progesterone and its metabolites as a neurogenic agent should take into account hormone concentrations.

In OPCs, progesterone enhances proliferation and differentiation *in vitro*, increasing their overall number and prompting OPCs to branch and mature into OLs [91,118,119,121,124–126]. Unlike findings in OPPs, progesterone's effects on OPC proliferation were not mimicked by the metabolite allopregnanolone, even at high concentrations [126]. Mechanistically, progesterone's effects on OPC proliferation and differentiation are mediated through PR signaling, as PR antagonists block these effects [126,127]. A recent study took these findings one step further and identified that, while embryonic OPCs express both PRα and PRβ, signaling through the PRβ receptor mediates progesterone's stimulatory effects on OPC proliferation and differentiation [127]. Activation of PRβ leads to upregulation of oligodendroglial genes ranging across the OL lineage, such as NG2, MBP, and CNPase. Indeed, an mPR-specific agonist did not alter OPC proliferation or differentiation, confirming that progesterone's effects on OLgenesis during development occur via a genomic mechanism [127].

As progesterone stimulates differentiation of OPCs, it is no surprise that adding progesterone to cultures *in vitro* increases the number of immature and mature OLs [98,111,115]. At the immature OL stage, progesterone promotes MBP expression, presumably indicating increased differentiation into mature, myelinating OLs [127] but does not increase pre-OL proliferation, as progesterone does not alter incorporation of BrdU into A007 or O4+ OLs [91,98]. Interestingly, the same dose of progesterone increases immature OL numbers to a greater extent in OLs cultured from 2–3-day old females compared to

males, suggesting the magnitude of sex steroid effects' depends on sex [98]. In addition to increasing numbers of immature OLs, progesterone also increases the number of mature, myelinating OLs (MBP+/CNPase+ immunoreactive cells), MBP and CNPase mRNA, and myelin protein expression [49,101,116,128–131]. Increases in MBP protein may be due to increased numbers of mature OLs, although there is some evidence to suggest that progesterone not only increases MBP+ cell numbers, but also MBP fluorescence intensity within a single mature OL *in vitro* [130]. The PR again is implicated mechanistically, especially for progesterone-induced increases in MBP [125,130]. In one study, selective antagonism of the PR did not alter progesterone-induced increases in the number of MBP+ cells, however, it did reduce overall MBP fluorescence intensity [130]. Furthermore, while progesterone agonists increased MBP expression, cell cultures from PR knock-out animals treated with progesterone no longer showed increases in MBP levels [125]. Future studies could aim to untangle whether increases in MBP and CNPase represent higher numbers of myelinating OLs or greater myelination by existing OLs. In addition, progesterone also interacts with other hormonal systems. Specifically, progesterone upregulates insulin-like growth factor-1 (IGF-1) and the IGF binding protein (IGFBP-6) in OPCs [49]. As we will describe in more detail below, IGF-1 broadly increases OLgenesis; therefore, this upregulation of IGF-1 may contribute towards progesterone-induced promotion of OL proliferation and differentiation. More work will be needed to disentangle direct effects on OLgenesis through the PR and indirect effects through hormonal interactions.

2.2.3. Androgens

Androgens are a class of steroid hormones derived from cholesterol by way of the progestogens. The androgen dehydroepiandrosterone (DHEA) is the primary androgen/estrogen precursor and is the least potent androgen [132]. DHEA can be converted to androstenedione (A4) or androstenediol (A5), both of which have weak to moderate androgen activity. Both A4 and A5 can be converted to testosterone (T), the primary circulating androgen in males [132]. T can be further metabolized by 5-α-reductase to the most potent androgen, dihydrotestosterone (DHT), locally in tissues such as the genitalia, skin, prostate gland, liver, and brain [132]. Interestingly, isolated myelin sheaths also display robust 5-α-reductase activity [133,134]. Notably, androgens are the precursors to estrogens. Via the enzyme aromatase, A4 is converted to estrone, while T is converted to estradiol. Although circulating levels of androgens are higher in males, both males and females produce androgens [135]. The zona reticularis of the adrenal cortex primarily produces the weak androgens DHEA, A4, and A5, while the gonads are the primary source of T. In males, androgen production begins early in development with a fetal surge of T that (primarily via conversion to DHT or estradiol) masculinizes the genitalia, brain, and other organs of the developing male [136]. Androgen levels then remain relatively low until puberty [135]. In females, androgen levels remain low until puberty, and the absence of androgens is a primary factor determining feminization of the genitalia, brain, etc. [136,137].

Androgens primarily act on the androgen receptor (AR), a member of the steroid hormone nuclear receptor family. Under basal conditions, the AR is sequestered in the cytoplasm; upon ligand-binding, the ligand-receptor complex is transported to the nucleus and dimerizes [138]. The DNA-binding domain of the AR selectively recognizes androgen response elements (AREs) in the genome, then exerts AR's effects on transcription by recruiting various coregulators and transcription factors [138]. In addition to these canonical genomic effects, evidence suggests that androgens can act via rapid second-messenger systems, including the PI3K/AKT, and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways [139,140].

The AR is expressed throughout the brain; however, very few studies have addressed whether androgens act directly on OLs via the AR or indirectly via actions on surrounding cell types. In rodents, one study examined the brains of rats ranging from

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embryonic day 20 to p86 and found no AR immunoreactivity in mature galactosylceramidase (GalC+) OLs at any age [141]. In contrast, one study of the prefrontal cortex of adult male and female rhesus macaque brains revealed that, while the majority of AR-expressing cells were astrocytes, roughly 5% of CNPase+ OLs colocalized with AR [142]. This species difference is reflected in transcriptomic analyses that suggest that AR expression is essentially undetectable in mouse OLs of any stage, while human OLs express AR to a low degree [42]. In addition, no studies have examined whether OLs express fast-acting, membrane-bound ARs.

Effects on oligodendrogenesis

Despite the low-to-absent expression of AR in OLs, several studies have indicated that manipulation of androgens have profound effects on OLs and myelin. Broadly, male rodents have greater OL cell density in white matter regions such as the corpus callosum, fornix, and spinal cord [68,143], although females have greater overall glial proliferation and cell death [68]. These sex differences in rodents arise as early as p5 and continue into adulthood [143]. Specific manipulation of androgens reveals that these sex differences occur, at least in part, due to the AR and not simply via conversion to estrogens. For example, gonadectomy with DHT replacement (which cannot be aromatized to estrogens) from puberty to adulthood increases Olig1 transcription in the male spinal cord over gonadectomized controls [144]. AR inhibition in males or DHT administration to females from p0 to p10 reverses the sex differences in corpus callosum OL density, and genetic deletion of AR in the CNS of males feminizes OL density and MBP expression throughout development and adulthood [143]. In humans, estimates of white matter volume correlate strongly with bioavailable T in male adolescents [145]. Moreover, this relationship is stronger in males with a polymorphism in the AR gene that is associated with greater androgen-dependent gene expression. Together, these studies suggest a direct role for the AR in promoting OL and myelin density in white matter tracts of male rodents and humans.

The mechanism by which androgens and ARs alter OLgenesis to bring about these sex differences remains somewhat unclear. Early work suggested that sex hormones alter OL proliferation and/or survival. Specifically, gonadectomy in adult males both decreases corpus callosum OL cell density and increases the number of subsequent mature BrdU+ OLs, suggesting a role for sex hormones in OPC proliferation and/or cell death [68]. However, application of T to rat-derived OPCs in culture does not alter BrdU incorporation, arguing against a direct role for androgens in OL proliferation [91].

Interestingly, androgens may promote OL cell death. Treating OLs in culture with T induces a small amount of OL cell death and potentiates excitotoxicity induced by exposure to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate [146]. This potentiation of excitotoxicity can be blocked by an AR antagonist, but not by aromatase inhibitors, suggesting that this effect is dependent on androgens and AR. The exact mechanism is unclear; while T potentiates AMPA and kainate receptor-induced calcium influx, T does not appear to alter the expression of glutamate receptor subunits in cultured OLs [146]. In line with this, exposure of cultured OLs to DHT decreases phosphorylated AKT expression and increases the number of OLs expressing caspase-3, a crucial mediator of apoptosis, suggesting that androgens can induce OL cell death [98].

In sum, there are many questions remaining in regard to androgens' role in OLgenesis. For example, do OPCs or OLs express cytoplasmic and/or membrane-bound ARs? Do androgens directly modulate OPC proliferation and differentiation, OL maturation, and OL survival, or does such modulation occur via surrounding neurons and/or astrocytes? Are these effects species-specific? Such questions can be definitively addressed with future well-controlled *in vitro* studies and transgenic models.

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

In this section, we discuss the role of amino acid-derived hormones and their receptors on OLgenesis. 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 a result, these hormones are typically stored in and secreted from vesicles and travel freely through the bloodstream, although some may be associated with binding proteins that aid in circulatory delivery and regulate bioavailability of the hormone. Because they are water-soluble, peptide and amine hormones typically act on cell surface receptors that utilize fast-acting second messenger systems [147].

Below, we detail the roles of peptides (including IGF-1, insulin, and prolactin), the amine hormone melatonin, and thyroid hormones in the regulation of the various stages of OLgenesis. OLs have been shown through both transcriptional and histological studies to express the receptors for each of these hormones. Interestingly, while the downstream actions of these receptors are considerably heterogeneous, activation of many of these receptors converge upon common signaling pathways, in particular the MAPK/ERK and PI3K/AKT signaling pathways. These pathways are broadly known to regulate cellular growth and survival [148,149], and indeed, while substantial gaps remain in our understanding of these hormones' effects across the OL lineage, each of these hormones has been shown to enhance OPC proliferation and/or OL survival.

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

IGF-1 is a 70 amino acid peptide that contributes to cell growth and proliferation, as well as cell survival [150–152]. This peptide is produced in the liver, and its secretion is stimulated indirectly by growth hormone (GH) and the growth hormone receptor (GHR) [153]. In the bloodstream, IGF-1 is largely bound to IGF-1 binding proteins [154]. In addition to hormonal delivery via the bloodstream, IGF-1 can be synthesized locally in the CNS by neurons and glia, including OLs [155,156].

While no studies to date demonstrate expression of GHR in OLs, all CNS cells, including OLs, express the IGF-1 receptor (IGF1R), a cell surface receptor with tyrosine kinase activity [151,157–159]. Ligand binding to IGF1R primarily induces the PI3K/AKT and the MAPK/ERK signaling cascades, which broadly inhibit apoptosis and promote mitogenesis, contributing to IGF-1's function in cell survival and tissue maintenance [160]. IGF-1 can also bind to the insulin receptor (IR) with lower affinity [161].

Effects on oligodendrogenesis

Overall, studies performed *in vitro* suggest that IGF-1 increases OLgenesis by enhancing OPC survival, promoting OPC differentiation, and inhibiting apoptosis of developing OLs. At the earliest progenitor stages, IGF-1 promotes the survival of neonatal-derived PSA-NCAM+ progenitors [162]. While IGF-1 alone does not promote proliferation of these cells [162], IGF-1 can act synergistically with growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF2) to promote NSC proliferation [162,163]. In addition, IGF-1 biases NSCs towards an OL fate; specifically, IGF-1 greatly increases OLgenesis from NSCs of the adult dentate gyrus, an effect driven by Noggin (NOG) and SMAD family member 6 (SMAD6) inhibition of bone morphogenic protein (BMP) signaling [164].

Specifically in the OL lineage, IGF-1 dose-dependently promotes OPC survival through PI3K-dependent inhibition of caspase-3 and subsequent apoptosis [165–167]. IGF-1 is therefore a potent survival factor for OPCs [166,168,169]. This effect persists past the proliferative phase of OL development, suggesting that IGF-1 promotes survival across the OL lineage [165,166].

While the anti-apoptotic effects of IGF-1 are well established, the mitogenic properties of IGF-1 on OPCs are less clear. Early experiments suggested that application of IGF-1 enhances proliferation of bipotential OPCs (O-2A) [170]. Subsequent studies further demonstrated that IGF-1 induces [3H] thymidine and BrdU incorporation in neonatal

cultured OPCs, indicating increased proliferation [171,172]. However, additional experiments have countered this, arguing that application of IGF-1 does not induce proliferation in OPCs derived from p7 mice or adult humans [165,173].

Differences between these experiments may be explained by OPC purity, experimental timing, or the age of animals from which cultures were derived. Such differences have broader implications for future studies of hormonal regulation of OLgenesis. First, an increasing number of studies demonstrate that glia release factors that modulate neurogenesis [174–176]; hence, contamination of OPC cultures or the use of mixed glial cultures could influence OLgenesis via indirect effects of IGF-1 on astrocytes or microglia, an important consideration for *in vitro* studies. Second, while co-applying BrdU and IGF-1 yields uptake of BrdU in OPCs, application of BrdU 24 hrs after IGF-1 treatment does not [165,171]. This suggests IGF-1 may induce a small and/or transient increase in OPC proliferation. Indeed, in experiments with co-application of IGF-1 and BrdU, IGF-1-induced proliferation is inhibited by PI3K, MAPK Kinase (MEK1), and Src-like tyrosine kinase inhibitors, which aligns with the mitogenic role of PI3K and MEK1 signaling in other cell types, as well as broader mitogenic properties of IGF-1 signaling [177,178]. Furthermore, the age at which primary cultures are obtained should be considered when comparing literature with cultured OPCs. OPC generation and migration through the developing rodent forebrain occurs in separate waves, with the final wave beginning around birth [179]. These OPCs compete with existing OL precursors and become the predominant OPC in many brain regions by p10. Although they maintain similar capacities for myelination, the responses of these separate OPC lineages to survival and proliferative factors are poorly understood. In fact, neonatally-derived OPCs may differ in their response to IGF-1, showing less IGF-1-induced differentiation to mature OLs as compared to their adult-derived counterparts [180]. This effect may be driven by differences in transcriptional profiles of proliferative and survival-related genes in neonatal- vs. adult-derived OPC cultures [180]. Lastly, culture conditions should be noted. Again, IGF-1 can act in concert with growth factors to promote proliferation of OPCs, but IGF-1 alone may have little effect [181].

Altogether, although the primary effect of IGF-1 is to inhibit apoptosis [172], IGF-1 may induce a small and transient PI3K/MEK1-dependent proliferative effect on OPCs. In support of this, loss of IGF1R specifically in Olig1-expressing cells results in a small decrease in proliferating NG2+ cells in young mice [169]. Additional experiments with, for example, live cell imaging on highly pure cultures to quantify cell cycle entry in real time would advance understanding of IGF-1's effects on OPC proliferation.

These studies demonstrate that IGF-1 stabilizes, and perhaps modestly amplifies, the OL progenitor pool. Further studies suggest that IGF-1 also promotes the commitment of glial progenitors to an OL fate. Indeed, early work posited that IGF-1 promotes the maturation of intermediate OPCs, as indicated by a higher percentage of O-2A progenitors progressing to immature OLs [170,182]. However, little else has been done to investigate whether and how IGF-1 promotes differentiation and maturation of OLs from OPCs beyond promoting cell survival. Similarly, few studies have addressed whether IGF-1 promotes the transcriptional or structural enhancement of myelinogenesis, either in development or during adulthood. While several studies demonstrate that IGF-1 upregulation increases myelin content *in vitro* and *in vivo* [182,183], this effect may be explained by greater numbers of surviving and differentiated OLs. One study has suggested that IGF-1 enhances transcription of myelin proteins from OLs [184]; however, this study utilized northern blots in mixed glial cultures. Studies with pure OL cultures and more quantitative methods of measuring transcription would strengthen our understanding of the effects of IGF-1 on OL maturation and myelinogenesis.

Ultimately, IGF-1 amplifies the number of mature, myelin-producing OLs in culture [157]. IGF-1 acts on multiple stages of OL development, from stem cell OL commitment to survival of mature OLs. This work in cell culture aligns well with *in vivo* studies in which IGF-1 signaling is either constitutively enhanced or reduced, leading to enhanced or reduced myelination, respectively. Specifically, mice deficient in GH or IGF-1 display

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widespread reductions in CNS myelination throughout development [185–187]. Conversely, mice overexpressing IGF-1 have larger brains with greater myelin content [188]. This is true as well when IGF-1 overexpression is restricted to astrocytes and OLs [189,190]. Loss of IGF1R specifically in either immature (Olig1+) or mature (PLP+) OLs results in developmental reductions in brain weight, OPC density, OL density, and myelination [169].

Each of these experiments utilized transgenic animals with constitutive transgene expression. Interestingly, while transgenic overexpression of IGF-1 produces a consistent elevation in brain weight and myelination throughout development, these measures stabilize by adulthood, suggesting there may be a developmental window and/or diminishing effects for IGF-1 on OLs and myelinogenesis [183,190]. While studies in adulthood are limited, one study assessed OL turnover in a rat model of adult-onset loss of GH and IGF-1 production [191]. Following loss of GH/IGF-1 signaling, the total number of proliferating (BrdU+) cells in the corpus callosum decreased, as well as the number, but not the percentage, of BrdU/PDGFR-α+ OPCs. Similar results were found for immature (GST-pi+ and adenomatous polyposis coli, APC+) OLs, suggesting a role for IGF-1 on OPC and OL survival in the adult brain [191]. Additional studies utilizing transgenic lines with temporally controlled genetic manipulation of IGF-1 signaling would greatly enhance our understanding of IGF-1's role in OLgenesis, specifically in adulthood. In addition, more detailed analyses of the mechanisms of IGF-1's effects on OPC differentiation, OL maturation, and myelination would aid in determining whether IGF-1's actions extend beyond survival and might enhance remyelination in disease contexts.

3.2. Insulin

Insulin is a 51 amino acid metabolic hormone that regulates glucose homeostasis by enhancing glycogen synthesis as well as the metabolism of other molecules such as lipids and certain amino acids [192]. In addition, insulin can promote cell division and growth, while also affecting behaviors such as food intake [193,194]. Insulin can be delivered to the CNS via circulation and transport across the blood brain barrier (BBB) [195]. However, insulin transcription has also been detected in neural and glial cultures, suggesting that insulin can act in both a hormonal and paracrine fashion on CNS cells [196,197]. Insulin binds to the insulin receptor (IR), a cell surface receptor with tyrosine kinase activity that, in the CNS, can be detected in the olfactory bulbs, the arcuate nucleus of the hypothalamus, and the hippocampus [198]. The IR is also expressed in all types of CNS cells, including OLs [42,199]. In addition, insulin can bind to IGF1R, albeit with a lower affinity [161].

Effects on oligodendrogenesis

Given the evolutionary relatedness of insulin and IGF-1 and the known crosstalk between their receptors, it is not surprising that insulin exhibits effects on OLgenesis that are similar to IGF-1's. Indeed, insulin promotes NSC differentiation towards the OL lineage, as well as OPC and OL survival [164,166,200]. Furthermore, similar to IGF-1, insulin increases the percentage of differentiated OLs from cultured p6-8 OPCs, suggesting enhanced OPC differentiation and/or OL survival [200]. Notably, at the high concentrations (e.g. 5000 ng/mL) used in some of these experiments, insulin can bind IGF1R and act via the mechanisms detailed above. However, dose response experiments suggest that insulin can also act independently of IGF1R at physiological concentrations [166]. In addition, insulin may have the ability to increase myelin basic protein (MBP) levels *in vitro*. Specifically, neonatal OPCs prepared from mixed glial cultures show an insulin dose-dependent increase in MBP protein [201]. However, in this study, insulin had no direct effect on MBP mRNA levels, and similarly to IGF-1, the observed increase in MBP protein may be due to enhanced differentiation and/or survival of OLs [201]. The specific actions of IR on OLgenesis remain poorly understood, and future studies should determine whether and how insulin modulates OL differentiation, survival, and maturation independent of

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IGF1R. In addition, given the high insulin levels that accompany disorders such as adult-onset type 2 diabetes, future work should also seek to determine whether insulin, either through IR or IGF1R, modulates adult OLgenesis in *in vivo* models.

3.3. Prolactin

Prolactin (PRL) is a 199 amino acid peptide that is best known for promoting lactation but also regulates diverse functions including sexual and parental behavior, immunomodulation, and osmoregulation [202]. Circulating PRL is produced by the anterior pituitary and can cross the BBB; however, PRL can also be produced locally by tissues such as the mammary glands, placenta, and brain (including regions such as the cortex, amygdala, thalamus, and hippocampus) [202–206]. PRL release by the anterior pituitary is environmentally modulated by a number of stimuli, including stress, daylength, and infant suckling, and neurally modulated by a number of signaling molecules that exhibit stimulatory (e.g. thyrotropin releasing hormone, oxytocin) or inhibitory (e.g. dopamine, somatostatin) regulation of PRL release [202,207,208].

The PRL receptor (PRLR) is a transmembrane receptor of the type 1 cytokine superfamily [202]. PRLR activation induces a kinase cascade primarily involving the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) signaling pathway, which contributes to cellular growth and proliferation [209]. PRLR can also act via PI3K and MAPK signaling pathways [202]. PRLR is expressed in several regions of the brain [210,211]; however, only one study to date has examined expression of PRLR in the OL lineage. Specifically, a subset of PDGFRα+ OPCs in the corpus callosum and spinal cord express PRLR [212]. This offers a potential mechanism by which PRL may alter OLgenesis in the CNS.

Effects on oligodendrogenesis

Although the entirety of PRL's actions on the OL lineage are not known, PRL may act on OPCs to enhance OLgenesis. In both adult mouse hippocampal and human embryonic NSC cultures, PRL stimulates NSC proliferation [213–215]. Furthermore, in OPC neurospheres (i.e. clusters of OPCs in culture) derived from the corpus callosum of adult female mice, PRL treatment increases the number and size of OPC neurospheres and increases the proportion of OLs in culture, suggesting that PRL enhances OPC proliferation and differentiation [212]. This is further supported by the observation that OPC proliferation, OL generation, MBP expression, and numbers of myelinated axons in the corpus callosum and spinal cord are all increased during pregnancy in mice, when PRL levels are elevated [212]. Furthermore, heterozygous loss of PRLR function attenuates the pregnancy-associated increase in OPC proliferation, while administration of exogenous PRL to virgin mice increases OPC proliferation [212]. Although this suggests that PRL can act either directly or indirectly on OPCs to promote proliferation, these findings are in contrast to work performed in OPC-enriched neurosphere cultures derived from the adult rat hippocampus (with 75% A2B5+ cells), in which seven days of PRL treatment had no effect on cell numbers and no effect on differentiation into MBP+ OLs [216]. Whether PRL acts on OPCs to enhance proliferation merits further investigation. Interestingly, PRL may exhibit some protective effects in demyelinating conditions [1,212]; however, beyond the few studies cited here, little else has been done to investigate whether and how PRL acts on the various stages of the OL lineage outside of disease contexts. Our understanding of the effects of PRL on OLgenesis would benefit from work with highly pure OL cultures, targeted disruption of PRL signaling in the OL lineage, and a closer investigation of the intracellular mechanisms that mediate PRL's direct and indirect effects on OPCs and OLs.

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3.4. Melatonin

Melatonin is an indolamine neurohormone derived from the amino acid tryptophan by way of serotonin. It is produced primarily by the pineal gland, although small amounts of melatonin may also be produced by other regions of the brain [217]. In addition, retinal and gut tissue can produce melatonin for local action [218]. Melatonin production is indirectly controlled by the suprachiasmatic nucleus (SCN), and retinal exposure to bright light indirectly inhibits melatonin production [219,220].

Melatonin is released into circulation and readily crosses the BBB. Melatonin binds two G-protein coupled receptors, melatonin receptor 1 (MT1) and 2 (MT2). MT1 is coupled to Gi and Gq/11 G proteins to inhibit adenylyl cyclase cAMP production and, hence, protein kinase A (PKA) activity [221]. Additionally, MT1 activation stimulates phospholipase C (PLC) activity and MEK/ERK signaling, and activates Kir3 inward-rectifying potassium channels. MT2 activates similar cascades as MT1, but also inhibits guanylyl cyclase [221]. Through these receptors, melatonin entrains central and peripheral tissues to the circadian rhythm, thereby regulating sleep-wake cycles, circadian hormone release, metabolism, and other daily or seasonal rhythms. In addition, melatonin exerts anti-inflammatory actions by normalizing pro-inflammatory cytokine levels, inhibiting inflammatory signaling cascades, and scavenging free radicals [222,223]. One study has shown that OLs express, to some extent, both MT1 and MT2, suggesting that melatonin may regulate OLgenesis [224].

Effects on oligodendrogenesis

Interest in melatonin's effects on OLgenesis began with studies demonstrating that melatonin is neuroprotective against white matter damage [225,226]. However, the mechanistic effects of melatonin on OLgenesis are largely unknown. In embryonic-derived NSC cell culture, application of melatonin over five days increases the percentage of MBP+ cells as compared to vehicle or PDGF application [227]. This suggests that melatonin may enhance NSC-derived OL differentiation or survival. Similar increases in OL numbers were found with melatonin application to NSC neurospheres cultured from the adult mouse subventricular zone [228].

Melatonin may also influence OL maturation. In studies of OL lineage cultures derived from neonatal rats, melatonin did not alter the number of immature (O4+) OLs but significantly increased the number of mature, myelinating (MBP+) OLs [224]. Moreover, similar effects were found *in vivo*. Specifically, neonatal rat pups subjected to uterine artery ligation to induce white matter damage were treated for 3 days with melatonin. While total (Olig2+) OL cell loss was not affected, mature (APC+) OL numbers were partially rescued in the cingulate and corpus callosum; this effect was thought to be through maturation, as melatonin treatment did not affect OL cell death [224]. Together, these results suggest that melatonin does not alter OL differentiation but increases OL maturation. However, these results may be muddled by the fact that, in the *in vitro* experiments, the cultured cells included astrocytes and microglia, which also express the melatonin receptors [224,229]. Specifically, the authors demonstrated that melatonin attenuates microglial activation [224]. Hence, it is unclear whether melatonin acts directly on OLs themselves or whether it acts on surrounding microglia to promote OL maturation indirectly. Experiments with highly pure cultures of OLs or OPCs could address this question.

Interestingly, one study more directly assessed the protective effects of melatonin on OL survival. Hypoxic conditions induce expression of caspase-3 in OLN-93 cells derived from p1 rats [230]. Applying melatonin to the culture medium attenuated hypoxia-induced caspase-3 expression, suggesting that melatonin acts on OLs to inhibit apoptotic cascades.

Overall, melatonin may regulate OLgenesis by promoting NSC commitment to the OL lineage, OL maturation, and OL survival. However, the number of studies supporting these claims are small, and several questions remain regarding both the physiological and

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mechanistic effects of melatonin on OLgenesis. For instance, does melatonin alter OPC proliferation? Does melatonin promote OL survival, and if so, what is the mechanism? In addition, given the expression of melatonin receptors on microglia and astrocytes, it remains unclear whether results from existing *in vitro* experiments are due to direct actions of melatonin on OLs or indirect actions on contaminating glial cells. Additional studies with melatonin receptor signaling disrupted specifically in the OL lineage would be interesting and beneficial. Further, given MT1 and MT2's known interactions with MEK/ERK proteins, future studies could, for example, test the mitogenic role of melatonin on OPCs and/or the role of MEK signaling in melatonin's regulation of OLgenesis.

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 and neuronal maturation, as well as overall organismal metabolism [231–234]. These two hormones, T3 and T4, are produced and released by the thyroid gland and are essential for the development and differentiation of cells, including OLs [48]. Their structures are based on the combination of two tyrosine amino acids that have been enzymatically modified to incorporate iodine molecules. T4 is the primary circulating TH, and enzymatic deiodination of T4 by type 2 deiodinase (Dio2) yields T3, the functionally active TH [231,232]. In the rat brain, Dio2 activity and corresponding levels of T3 increase after gestation and peak just prior to weaning [233–235]. THs cross the BBB into the CNS via various membrane transporter proteins [236].

Thyroid hormone receptors (TRs) are part of the nuclear receptor subfamily, and they bind either as homodimers or heterodimers to thyroid response elements (TREs) in DNA to alter gene expression [237]. In fact, TR binding to TREs occurs primarily due to heterodimerization with the retinoid X receptor (RXR) [238]. Interestingly, in the absence of TH or under conditions of low TH, unliganded TRs form a complex with co-repressor proteins, inhibiting gene transcription [237]. There are two primary classes of TR isoforms: TRα and TRβ, which are highly homologous but differ in their N-termini and their distribution across tissues in the body [239]. TRα and TRβ each produce several splice variants, three of which bind T3: TRα1, TRβ1, and TRβ2. Although nuclear receptors traditionally act at the level of transcription, TRs can also have non-genomic effects. For example, both TRα1 and TRβ2 can act via PI3K/AKT pathways to exert rapid effects [240,241]. Lastly, in addition to nuclear TRs, THs can bind to a transmembrane receptor, the integrin $\alpha v\beta 3$ dimeric receptor, to exert non-genomic effects [242].

Nuclear TRs are expressed in OLs, both *in vitro* and *in vivo* [243–246]. Interestingly, expression differs across the OL lineage [247]. Specifically, OPCs express TRα, while differentiated OLs express both TRα and TRβ [243,244,248,249]. In addition, TRs dimerize with other nuclear receptors expressed in OLs [250], including vitamin D3 receptors, peroxisome proliferator-activated receptors, and the RXR [251–253]. Pre-myelinating, immature OLs from p0-p2 rat pups also express the transmembrane receptor, $\alpha v\beta 3$ [254], which regulates OL differentiation through a non-genomic pathway; in particular, binding $\alpha v\beta 3$ activates PI3K/Akt and Erk pathways that help translocate TRs from the cytosol to the nucleus [255]. Together, expression of these receptors enables THs to affect OLgenesis [256].

Effects on oligodendrogenesis

At the earliest stages of the OL lineage, THs regulate proliferation, differentiation, and cell death of both developing and adult NSCs. For example, TH is required for embryonic NSC maintenance and proliferation; pharmacological depletion of TH inhibits proliferation, and TH binding to the $\alpha v\beta 3$ receptor increases proliferation of cortical progenitors [257]. Excessive TH however can also have a negative effect on embryonic NSC proliferation, [128], suggesting there may be an optimal amount of TH for NSC proliferation. In addition to effects on proliferation, T3 also promotes embryonic NSC

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differentiation *in vitro*, promoting cells to differentiate toward a mixed glial fate [258]. Specifically, OPC quantities increase three-fold in the presence of T3 [259]. This effect requires the presence of the glycoprotein, transferrin, which increases TRα1 expression [260]. Similar effects on OLgenesis are observed in adult-derived NSCs. Consistent with the inverted U function of TH action, hyperthyroidism reduces NSC proliferation. Furthermore, treating adult-derived NSCs with T3 favors OPC differentiation [261,262]. Lastly, T3 acts not only on NSCs; treating oligodendrocyte pre-progenitors (OPPs) (PSA-NCAM+) isolated from newborn rats with T3 enhances FGF-2-mediated cell growth [258].

TH also modulates OPC proliferation and differentiation. In particular, T3 prompts OPCs to exit the cell cycle and differentiate into mature OLs [48,263,264]. The mechanisms of this switch are only partially elucidated and appear to depend in part on TRs [249,265–267]. T3 binding to TRα1 leads to complete arrest of OPC proliferation *in vitro* [268], and the absence of TRα1 results in continued proliferation of OPCs [266]. TR*α*2 mRNA, which encodes a dominant-negative form of TR*α*, also decreases as OPCs proliferate, which may create a permissive state for TRα1 action and subsequent OPC differentiation [249]. Thus, several forms of TRα are involved in prompting OPCs to exit the cell cycle. TR-dependent effects on OPC differentiation are a bit more complex. Given that TRβ expression is confined to differentiated OLs, it is suggested that TRα receptors facilitate the effect of TH on OPC differentiation, while TRβ aids in terminal differentiation into mature OLs [249]. Indeed, overexpression of TRα accelerates OPC differentiation in culture [267]. Yet, applications of TRβ agonists and TRβ overexpression also increase OPC differentiation; it is unclear if these effects are truly TRβ dependent or whether this exogenous upregulation of TRβ acts at the same TREs as TRα [249,265]. Importantly, these studies have all been conducted *in vitro*; *in vivo* studies will be necessary to confirm both the effects of TH on OPC development, and the role of specific TR variants. In addition, T3-induced OPC differentiation could also be enhanced through interactions with other OL differentiation factors such as IGF-1, among others [48,269,270]. For example, TH levels are positively associated with IGF-1 levels [269,271], and IGF-1 is upregulated following TH exposure in adult rat brains [269].

THs also induce OL maturation and alter OL morphology [261,272–277]. Specifically, THs promote both morphological and functional maturation of OLs through interactions with MBP promoter regions and transcriptional regulation of other genes such as myelin oligodendrocyte glycoprotein (MOG) and glutamine-synthase [272,274–277]. Consistent with these findings, TH deficiency shortens the elongation process of mature OLs [273] and delays expression of MBP and CNPase, a myelin associated enzyme [274]. T3 can also act in conjunction with 9-cis retinoic acid (which binds to RXR) to increase the number of premyelinating OLs, increase OL morphology complexity, and increase MBP expression [278,279]. Interestingly, in rodents, OL maturation is only influenced by T3 in the first 3 weeks of life after birth [280]. During that time, THs also enhance OL survival [281]. This effect may occur through TH's ability to regulate survival-specific growth factors such as neurotrophin-3 (NT-3) and IGF-1 [282–285]. Outside of this time window, OLs no longer require TH to survive [281]. These findings suggest that TH may no longer have a role in OL maturation and survival in adulthood under physiological conditions. These differences in TH action across the lifespan are highly unexplored and are a fruitful area for future study.

Overall, THs potentiate OLgenesis along the OL lineage, from specification of NSCs towards an OL fate, to cell cycle arrest and differentiation of OPCs, to maturation of immature OLs and increasing myelination in mature OLs.

4. Non-classical hormones: Neurohormones, neuromodulators, and neurotransmitters

This review has focused on "classic" endocrine hormones; however, many hormones (including some discussed here) not only are produced in the CNS, but also can act in a paracrine fashion in the brain via synaptic or extrasynaptic transmission. Future research

could investigate how neuropeptides that are not deemed to be classic hormones such as corticotropin releasing hormone (CRH), the pseudo-hormones epinephrine (EP) and norepinephrine (NE), and secretin hormones such as vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating peptide (PACAP), affect OLgenesis. Existing literature on CRH is limited and only indirectly applies to OLgenesis [286,287], although CRH elevates cAMP levels in OPCs [288]. Existing research regarding EP and NE is more abundant, and adrenoreceptors are found across the OL lineage. Specifically, the α1-adrenergic receptor is prevalent in both OPCs and differentiated OLs [42,289,290] and β1-adrenergic receptor expression has been detected in OPCs and GalC+ OLs [42,291]. NE induces α1-adrenergic receptor-dependent second messenger signaling [289]. However, signaling through α1 receptors does not affect OPC proliferation [292], and the effects of these receptors on OLgenesis remain unresolved. Activation of β adrenergic receptors inhibits proliferation and induces differentiation of OPCs [292]. Future research should continue to investigate how catecholamines, CRH, and other neuromodulators affect OLgenesis throughout the postnatal and adult period and if effects are observed following injury.

Interestingly, there is a growing body of literature suggesting the peptides VIP and PACAP may also influence OLgenesis. These homologous proteins are members of the secretin superfamily and have been increasingly implicated in a diverse set of activities in the body, such as regulation of circadian rhythms, smooth muscle tone, immune function, and cell proliferation [293,294]. Both VIP and PACAP are expressed in many regions of the brain [295]. VIP and PACAP bind to the VIP/PACAP receptors, VPAC1 and VPAC2; in addition, PACAP binds an additional receptor, PAC1, with high affinity [294]. While no studies have demonstrated protein-level expression of VPAC1 or VPAC2 in OPCs or OLs, RNA transcriptomic analyses suggest that VPAC2 is enriched in mouse OPCs, but not mature OLs [42]. In addition, PAC1 mRNA and PAC1 protein expression have been detected in immature to mature OLs [296,297]. Thus, VIP and/or PACAP may influence the OL lineage. Consistent with this, early and intermediate OPCs respond to VIP and to PACAP by elevating cAMP levels [288]. While the specific actions of these peptides on OLgenesis are largely unknown, evidence suggests that PACAP increases OPC proliferation [297]. PACAP may also delay myelination both *in vitro* and *in vivo* [297,298]. Given that the expression of receptors for VIP and PACAP change over the course of the OL lineage, additional research with selective agonists and antagonists for each receptor would greatly aid in our understanding of the role of these peptides in the various stages of OLgenesis.

5. Future Directions

In this review, we have discussed the roles of numerous hormones in the regulation of OLgenesis; however, there are many avenues for future work in this field. For example, much of the work we described built upon investigations *in vitro* that utilize classic, but limited, pharmacological approaches and raw counts of cells from discrete, but somewhat arbitrary, time points. In addition, many of the studies we described focused on only a particular timepoint in the OL lineage, often through the use of just one cellular marker. Future studies will require careful examination across the OL lineage, utilizing multiple markers of OL staging and ideally looking at markers for proliferation (such as BrdU) and survival (such as caspase-3) all within the same study. This will enable optimal interpretation of a hormone's effects on OLs, and will allow us to determine whether changes in numbers of OPCs or mature OLs are due to proliferation, differentiation, or survival.

Furthermore, for most of the hormones discussed, there remain substantial gaps in our understanding of the fundamental mechanisms governing the intracellular response to the hormone and the subsequent fate of the OL lineage cell. These gaps could be addressed with carefully controlled *in vitro* experiments. In particular, the field is ripe for studies that utilize modern techniques for targeted manipulation of hormones and their receptors and precise measurement of proliferation, differentiation, and myelinogenesis

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to dissect the role of these hormones on OPCs, OLs, or surrounding neurons, astrocytes, and microglia.

Similarly, *in vivo* work is limited, especially outside of disease contexts, and we have little understanding of whether and how hormones affect OPCs and OLs differently based on brain region, cellular age, or organismal age. In many cases, the *in vivo* experimental designs we describe utilized constitutive overexpression/deletion of hormones or receptors, which offer little temporal resolution and may be complicated by widespread alterations to the developmental trajectory of the organism. In addition, most of these manipulations were not restricted to OL lineage cells. Generating model organisms with genetic manipulations specifically within the various stages of the OL lineage would offer greater insight into direct hormonal modulation of OLgenesis, and designing these manipulations to be temporally controlled would present the opportunity to test hormonal effects on OLgenesis across the full extent of the lifespan, from early life to transitional periods such as puberty, and throughout adulthood and aging. Ultimately, understanding the direct vs. indirect effects of hormones on OLgenesis *in vivo* will provide greater understanding not only of the mechanisms of hormonal action, but also of the suitability of hormonal interventions in providing direct, as opposed to off-target, effects in the CNS.

Lastly, while we have detailed the effects of many different hormones on OLgenesis, this is only a small fraction of the hormones that regulate development and adult plasticity. In the previous section, we described the few studies that focus on hormones that act in a paracrine fashion in the brain. Yet, many hormones remain to be explored. Our review has focused on the existing literature, but the absence of evidence does not imply that such hormones have no role in regulating OLgenesis.

5. Conclusions

Hormones regulate nearly every stage of human development, and in adulthood, their levels can be modulated by a host of conditions, including stress, pregnancy, menopause, and aging. These hormonal fluctuations influence the brain and behavior, in part by altering the birth and development of new cells. As we have described in this review, hormonal modulation of plasticity extends beyond neurogenesis and into the realm of glia. Overall, it is clear that hormones across many classes exert robust effects on OLgenesis, not only during development, but also in adulthood. Many of these hormones, including IGF-1, thyroid hormones, and the sex hormones, act to increase OPC differentiation and enhance maturation of mature, myelinating OLs through both direct and indirect mechanisms (Figure 2). Clearer insight into the mechanisms governing hormonal regulation of OLgenesis will enable better understanding of experience-dependent myelination in the human brain, and has important implications for myelin repair in a range of disorders, which we describe in our companion review in this issue [1].

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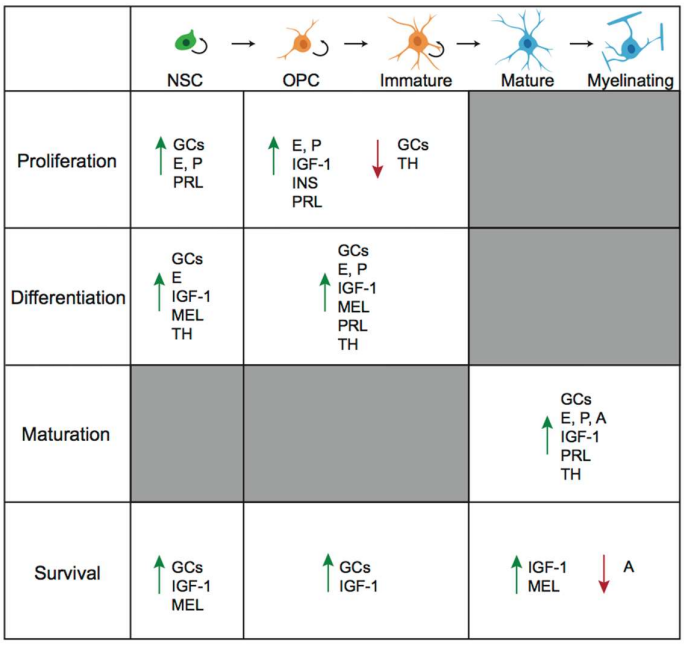

Figure 2. OLgenesis is differentially affected by various classes of hormones. Hormones can affect proliferation, differentiation, maturation, and survival across the OL lineage. Green arrow = promote, Red arrow = downregulate. GC = glucocorticoids, E = estrogens, P = progestogens, A = androgens, IGF-1 = insulin-like growth factor-1, INS = insulin, PRL = prolactin, MEL = melatonin, TH = thyroid hormones.

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Appendix – List of Abbreviations

A4
: Androstenedione

A5
: Androstenediol

AKT
: Protein kinase B

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

AR
: Androgen Receptor (nuclear)

ARE
: Androgen Response Element

BBB
: Blood Brain Barrier

BDNF

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Brain Derived Neurotrophic Factor

BMP
Bone Morphogenic Protein

BrdU
Bromodeoxyuridine

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

CNS
Central Nervous System

Cort
Corticosterone

CREB
cAMP response element-binding protein

CreER
Cre recombinase

CRH
Corticotropin Releasing Hormone

CSF
Cerebrospinal Fluid

Dex
Dexamethasone

DHEA
Dehydroepiandrosterone

DHP
Dihydroprogesterone

DHT
Dihydrotestosterone

Dio2
Type 2 Deiodinase

E2
17-β estradiol

EAE
Experimental Autoimmune Encephalomyelitis

EGF
Epidermal Growth Factor

EP
Epinephrine

ER
Estrogen Receptor (nuclear)

ERK
Extracellular signal-regulated kinase

FGF
Fibroblast Growth Factor

GalC
Galactosylceramidase

GC
Glucocorticoid

GH
Growth Hormone

GHR
Growth Hormone Receptor

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GPCR/GPR
: G-protein Coupled Receptor

GPDH
: Glycerol Phosphate Dehydrogenase

GST-pi
: Glutathione-S-Transferase-pi

GR
: Glucocorticoid Receptor (nuclear)

GREs
: Glucocorticoid Receptor Elements

HPA
: Hypothalamic-Pituitary-Adrenal

HSD
: Hydroxysteroid Dehydrogenase

IGF-1
: Insulin-Like Growth Factor-1

IGF1R
: Insulin-Like Growth Factor-1 Receptor

IGFBP
: Insulin-Like Growth Factor Binding Protein

IR
: Insulin Receptor

LPC
: Lysophosphatidylcholine

MAPK
: Mitogen-activated protein kinase

MBP
: Myelin Basic Protein

MCT8
: Monocarboxylate Transporter 8

MEK
: Mitogen-activated protein kinase kinase

MOG
: Myelin Oligodendrocyte Glycoprotein

MP
: Methylprednisolone

mPR
: Membrane Progesterone Receptor

MR
: Mineralocorticoid Receptor

MS
: Multiple Sclerosis

MT1
: Melatonin Receptor 1

MT2
: Melatonin Receptor 2

mTOR
: Mammalian Target of Rapamycin

NDRG1
: N-myc Downstream-Regulated Gene 1

NE

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NE
: Norepinephrine

NG2
: Neural/glial antigen 2

NPC
: Neural Progenitor Cell

NSC
: Neural Stem Cell

NT-3
: Neurotrophin-3

O2A
: Bipotential oligodendrocyte-type 2 astrocyte progenitor cells

OL
: Oligodendrocyte

OLgenesis
: Oligodendrogenesis

Olig1
: Oligodendrocyte transcription factor 1

Olig2
: Oligodendrocyte transcription factor 2

OPC
: Oligodendrocyte Precursor Cell

OPP
: Oligodendrocyte Pre-Progenitor

PACAP
: Pituitary Adenylate Cyclase Activating Peptide

PDGF
: Platelet-Derived Growth Factor

PDGFRα
: Platelet-Derived Growth Factor Receptor Alpha

PGRMC1
: Membrane-associated Progesterone Receptor Membrane Component 1

PI3K
: Phosphatidylinositol 3-kinase

PKA
: Protein Kinase A

PLC
: Phospholipase C

PLP
: Proteolipid protein 1

PR
: Progesterone Receptor (nuclear)

PRL
: Prolactin

PSA-NCAM
: Polysialylated Neural Cell Adhesion Molecule

PTSD
: Post-Traumatic Stress Disorder

RRMS
: Relapsing-Remitting MS

RXR
: Retinoid-X Receptors

SCI
: Spinal Cord Injury

SGK1
: Serum Glucocorticoid Regulated Kinase 1

T
: Testosterone

T3
: Triiodothyronine

T4
: Thyroxine

TH
: Thyroid Hormone

THP
: 3α,5α,Tetrahydroprogesterone

TR
: Thyroid Hormone Receptor (nuclear)

TRE
: Thyroid Response Element

VIP
: Vasoactive Intestinal Peptide

VPAC1
: Vasoactive Intestinal Peptide Receptor 1

VPAC2
: Vasoactive Intestinal Peptide Receptor 2

YFP
: Yellow Fluorescent Protein

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