REVIEW

Progesterone effects on the oligodendrocyte linage: all roads lead to the progesterone receptor

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Abstract

A new role has emerged for progesterone after discovering its potent actions away from reproduction in both the central and the peripheral nervous system. The aim of the present report is to discuss progesterone's mechanisms of action involved in myelination, remyelination and neuroinflammation. The pivotal role of the classic progesterone receptor is described and evidence is compiled about progesterone's direct effects on oligodendrocyte linage and its indirect effects on oligodendrocyte precursor cell differentiation by decreasing the neuroinflammatory environment.

Key Words: *progesterone; progesterone receptor; oligodendrocyte differentiation; myelination; remyelination; neuroinflammation*

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doi: *10.4103/1673-5374.262570*

Received: *February 20, 2019*
Accepted: *April 25, 2019*

Introduction

Progesterone is a well-known sex hormone that plays a pivotal role in reproductive tissues. However, a new role has emerged for the steroid after discovering its potent actions away from reproduction in both the central nervous system (CNS) and the peripheral nervous system (PNS) (Schumacher et al., 2012). Progesterone effects beyond reproduction include myelin formation, neuroprotection, anti-inflammatory actions, neurogenesis regulation, preservation of mitochondrial function and regulation of mood, memory and cognition (Brinton, 2013; De Nicola et al., 2018). The aim of the present report is to discuss progesterone mechanisms of action involved in myelination, remyelination and neuroinflammation. We not only reviewed the preponderant role of progesterone receptor (PR) in the mentioned process but also described the pro-myelinating actions of its reduced derivative tetrahidroprogesterone (THP), a potent agonist of the $GABA_A$ receptor. Finally, attention is drawn to the fact that progesterone actions could be direct on oligodendrocyte linage or alternatively indirect through the downregulation of the inflammatory process.

It is important to establish the differences between myelination and remyelination. While myelination addresses the formation of myelin during development, remyelination is related to myelin repair in the adult nervous system. In the CNS mature oligodendrocytes in both processes derive from the differentiation of oligodendrocyte precursor cells (OPC), but adult OPC are indeed distinct from the perinatal ones (Fancy et al., 2011). For example, the proliferation rate of perinatal OPC is higher than the one found in adult OPC (Fancy et al., 2011). Another important difference between myelination and remyelination is referred to the signals that drive the process. Myelination is mainly driven by axons signals while remyelination is induced by neuroinflammation (for review see Fancy et al., 2011).

Effect of Progesterone on Myelination and Remyelination in the Peripheral Nervous System

Progesterone pro-myelinating effects were first demonstrated 20 years ago in the PNS and are summarized in **Table 1**. In this regard, in co-cultures of Schwann cells and dorsal root ganglia neurons progesterone accelerates myelination and enhances the rate of myelin synthesis (Chan et al., 1998). Progesterone also stimulates myelination in the regenerating sciatic nerve after a cryolesion (Schumacher et al., 2012) and increases both the number of Schwann cells and the g-ratio of myelinated fibers during regeneration of the facial nerve (Chavez-Delgado et al., 2005).

In the nervous system progesterone can be converted into dihidroprogesterone (DHP) by the enzyme 5α-reductase and subsequently DHP can be reduced to THP by the enzyme 3α-hydroxysteroid oxidoreductase (**Figure 1**) (Schumacher et al., 2012; Melcangi and Panzica, 2014). These conversions contribute to the pleiotropic mechanisms of progesterone since DHP interacts with the PR and THP is a potent positive modulator of the $GABA_A$ receptor (Lambert et al., 2001). In the PNS, both Schwann cells and dorsal root ganglia neurons express not only the PR and $GABA_A$ receptor but also the mentioned enzymes, which metabolize progesterone into THP (Melcangi et al., 2011). As demonstrated in several experimental models, progesterone and its derivatives reverse the frequency of myelin morphological abnormalities in peripheral nerves during aging (Azcoitia et al., 2003) and diabetic disease (Melcangi et al., 2011).

Progesterone and its reduced metabolites promote the synthesis of glycoprotein zero (P0) and the peripheral myelin protein 22 (PMP22) by stimulating the expression of key transcription factors in the myelination program of Schwann cells such as Krox-20, FosB, Sox 10 and Krox 24 (Guennoun et al., 2001; Mercier et al., 2001). Progesterone, DHP and

Table 1 Effects of progesterone and THP on myelination, remyelination and neuroinflammation.

Steroid	Experimental model	Studied effects	Accions	Reference
Prog	Cultures of Schwann cells and DRG neurons	Myelination in PNS	Accelerates myelination and enhances the rate of myelin synthesis	Chan et al., 1998
Prog	Lesion of facial nerve	Remyelination in PNS	Increases the number of Schwann cells and the g-ratio	Chavez et al., 2005; Sclumacher et al., 2012
Prog, DHP, THP	Aged mice	Remyelination in PNS	Reverses morphological myelin abnormalities	Azcoitia et al., 2003
Prog, DHP, THP	Diabetic mice	Remyelination in PNS	Reverses morphological myelin abnormalitie	Melcangi et al., 2011
Prog, DHP, THP	Cultures of Schwann cells and adult sciatic nerve	Myelination in PNS	Increases P0 and PMP22	Guennoun el al., 2001; Mercier et al., 2001; Magnaghi et al., 2007
THP	Floating spheres cultures	Myelination in CNS	Increases OPP proliferation	Gago et al., 2004
Prog	Cerebellar organotypic cultures	Myelination in CNS	Increases OPC proliferation, the number of mature oligodendrocytes and MBP expression	Ghoumari et al., 2003, 2005
THP	Cerebellar organotypic cultures	Myelination in CNS	Increases MBP expression	Ghoumari et al., 2003, 2005
Prog	Ethidium bromide-induced demyelination	Remyelination in CNS	Increases the number of remyelinated axons	Ibanez et al., 2004
Prog	Spinal cord injury	Remyelination and neuroinflammation in CNS	Increases OPC differentiation, myelin protein expression and OPC survival. Decreases the number of astrocytes and microglial cells and pro-inflammatory cytokines. Promotes anti-inflammatory microglia	Labombarda et al., 2009, 2011; Jure et al., 2018
Prog Nestorone	Lysolecithin-induced demyelination in cerebellar organotypic cultures	Remyelination in CNS	Increases MBP expression and OPC migration	Hussain et al., 2011
Prog Nestorone	Cuprizone-induced demyelination	Remyelination and neuroinflammation in CNS	Increases myelin protein expression and the number of oligodendrocytes. Decreases the number of microglial and astrocytes	El-Etr et al., 2015
THP	Trangenic mice of Alzheimer's disease	Remyelination in CNS	Promotes the regeneration of white matter	Brinton et al., 2013
Prog THP	EAE model	Remyelination and neuroinflammation in CNS	Increases remyelination; Decreases pro-inflammatory cytokines and microglial cells.	Garay et al., 2012; Noorbakhsh et al., 2014
Prog	Cuprizone-induced demyelination	Neuroinflammation in CNS	Promotes the switch from pro-inflamatory to anti-inflammatory microglia	Aryanpour et al., 2017

Prog: Progesterone; DHP: dihidroprogesterone; THP: tetrahidroprogesterone; DRG: dorsal root ganglia; CNS: central nervous system; PNS: peripheral nervous system; EAE: experimental autoimmune encephalomyelitis; OPC: oligodendrocyte precursor cells; MBP: myelin-basic protein; OPP: oligodendrocyte pre-progenitors; P0: glycoprotein zero; PMP22: peripheral myelin protein 22.

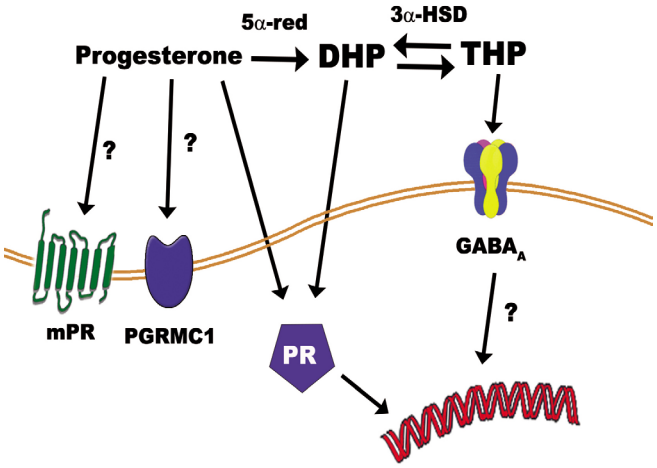

Figure 1 Progesterone pleiotropic effects are mediated *via* the progesterone receptor (PR), progesterone membrane receptor (mPR), and the membrane-associated protein progesterone receptor-membrane component-1 (PGRMC1).
Progesterone can be reduced to dihidroprogesterone (DHP) by the enzyme 5α-reductase (5α-red). DHP can also activate PR. DHP is subsequently converted into tetrahidroprogesterone (THP) by the enzyme 3α-hydroxysteroid oxidoreductase (3α-HSD). THP activates the GABA$_A$ receptor.

THP increase Po and PMP22 expression in the adult sciatic nerve and in Schwann cell cultures (Melcangi et al., 2011) using different mechanisms of action (Magnaghi et al., 2001). On the one hand, progesterone, DHP and THP enhance mRNA levels of P0 involving PR as the potent PR-antagonist RU-486 abolishes P0 up-regulation (Magnaghi et al., 2001). Since the enzyme 3α-hydroxysteroid oxidoreductase is bi-directional (Rupprecht et al., 1996) the action of THP (which does not bind PR) may be due to its retro-conversion into DHP. On the other hand, neither progesterone nor DHP increase the mRNA levels of PMP22 (Magnaghi et al., 2001). Only THP stimulating the GABA$_A$ receptor is able to modify PMP22 expression. Altogether, these results indicate that both PR and GABA$_A$ receptor are involved in the regulation of PNS myelination.

Involvement of Progesterone in Developmental Myelination in the Central Nervous System

Progesterone effects on myelin formation in the PNS are

also described in the CNS. **Table 1** shows progesterone actions on the CNS. Schumacher's group was the first to describe progesterone actions on developmental myelination in the oligodendroglial linage (Gago et al., 2001, 2004) and organotypic cultures (Ghoumari et al., 2003, 2005). In this regard, progesterone and THP are synthetized by oligodendrocyte pre-progenitors (OPP) during their differentiation into mature oligodendrocytes and increase their proliferation in cultures obtained from floating spheres (Gago et al., 2001; 2004). Progesterone increases the proliferation of OPP through its conversion to THP, while THP enhances their proliferation activating the $GABA_A$ receptor (Gago et al., 2004). These progenitors release GABA, which is involved in their proliferation, generating an autocrine mechanism of propagation. In this respect, THP and GABA in neural progenitor cells depolarize the plasma membrane and open the voltage-dependent L-type Ca^{2+} channel. Calcium influx leads to a downstream signaling pathway *via* Ca^{2+}-dependent kinase which activates the cyclic AMP-responsive element-binding protein 1 and genes that regulate the cell cycle (Wang et al., 2005).

In cerebellar organotypic cultures, while progesterone increases OPC proliferation, the number of mature oligodendrocytes and myelin-basic protein (MBP) expression, THP only enhances MBP synthesis (Ghoumari et al., 2003; 2005). In OPC, which are more differentiated than OPP, progesterone and THP enhance MBP levels involving mainly PR and to a lesser extent the $GABA_A$ receptor (Ghoumari et al., 2003). PR plays a key role in OPC as no progesterone pro-myelinating effects have been observed in PR knockout mice (Ghoumari et al., 2003; 2005). These results suggest that THP modulates OPP proliferation but as cells become more and more differentiated progesterone may drive this process *via* PR.

Effect of Progesterone on Remyelination in the Central Nervous System

The prolonged administration of progesterone enhances the number of remyelinated axons in a model of toxin-induced demyelination in the brain of aging rats (Ibanez et al., 2004). In the mentioned model, the rate of remyelination is age-dependent and the process is efficient only in young rats. In this scenario, progesterone does not modify the remyelination process of young animals but exerts pro-myelinating effects on aged rats, where remyelination occurs with sub-optimal efficiency (Ibanez et al., 2004).

De Nicola's group was the first to demonstrate that progesterone indeed differentiates proliferating OPC into mature oligodendrocyte after spinal cord injury (SCI) (Labombarda et al., 2006, 2009; Jure et al., 2019). Prolonged progesterone administration during 21 days after SCI increases the number of mature oligodendrocytes and enhances the expression of both mRNA and protein of MBP and proteolipid protein (Labombarda et al., 2009). During the acute phase after SCI, progesterone treatment enhances OPC survival and stimulates mitotic OPC to differentiate into mature oligodendrocytes after 3 weeks of treatment (Labombarda et al., 2009, 2015).

The differentiation program is a regulated process which involves the finely-tuned interplay of transcription factors and epigenetic modifiers (Huang et al., 2013). This program involves the synchronization of transcriptional inhibitors downregulation with the upregulation of transcriptional activators (Liu and Casaccia, 2010). The downregulation of the transcriptional inhibitors opens a window of opportunity for the activators to enhance and drive remyelination. It has been recently published that after SCI both the transcriptional inhibitors of the differentiation program and the transcriptional activators are down-regulated (Jure et al., 2019). Thus OPC missed the window of opportunity to differentiate after SCI. However, after progesterone treatment, the number of OPC which express the transcriptional activators of the differentiation program are up-regulated and the process is stimulated (Jure et al., 2019). Specifically, the expression of mRNA levels of the key activators of the differentiation program such as Olig2, Nkx2.2, Sox10 and Mash1 is enhanced after progesterone administration (Jure et al., 2019). The mentioned transcription factors are well-known players in OPC commitment to mature oligodendrocytes (Huang et al., 2013; Mitew et al., 2014).

Additionally, a recent report using MRI technology has demonstrated that progesterone reduces secondary damage and preserves white matter volume after spinal cord contusion (Garcia-Ovejero et al., 2014). They have shown that progesterone treatment increases the number of mature oligodendrocytes. After the CatWalk gait analysis, they found that the steroid improves locomotor outcome after SCI (Garcia-Ovejero et al., 2014).

Several publications have supported these results showing progesterone remyelintation properties. Progesterone and nestorone (a potent PR agonist) increase MBP expression after lysolecithin-induced demyelination in cerebellar slices (Hussain et al., 2011) and enhance remyelination after cuprizone treatment in corpus callosum and cerebral cortex (El-Etr et al., 2015). Remyelinating progesterone and nestorone actions are mediated by PR since the use of PRKO transgenic mice inhibits progesterone effect in the mentioned models (Hussain et al., 2011; El-Etr et al., 2015). Notably, in cerebellar organotypic cultures Nestorone enhances not only the maturation of OPC but also the migration of these progenitors towards demyelinating axons after lysolecithin application (Hussain et al., 2011). On the contrary, medroxyprogesterone acetate (MPA) has no effect neither on MBP immunoreactivity nor on the replenishment of oligodendrocytes in the mentioned demyelinated cerebellar culture (Hussain et al., 2011). It is known that glucocorticoids are not involved in the remyelination of cerebellar slices (Hussain et al., 2011). As a consequence, MPA remyelinating failure may be due to binding not only to PR but also to GR.

Finally, with regard to the effects of THP on remyelination in the CNS, Brinton (2013) has demonstrated that the steroid enhances myelin protein expression and promotes regeneration of white matter in a transgenic mice model of Alzhei-

mer's disease. On the other hand, in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS), progesterone and THP attenuate neurological deficits and increase remyelination (Yu et al., 2010; Garay et al., 2012). An outstanding study reported a significant decrease in the rate of relapses in MS patients during pregnancy and a significant increase during the first three months post-partum by comparison to the relapse rate observed during the year prior to pregnancy (Vukusic et al., 2009). Based on these results, a clinical trial began in 2009 (POPART´MUS – Reference number NTC00127075) using a synthetic progestin (nomegestrol acetate) to prevent post-partum relapses in women with MS. The POPART´MUS study is still ongoing.

Possible Mechanisms for the Pro-Myelinating Effect of Progesterone

The precise mechanism in myelin formation in the CNS is controversial. As already mentioned PR is involved in developmental myelination (Ghoumari et al., 2003, 2005) and remyelination (Hussain et al., 2011; El-Etr et al., 2015; Labombarda et al., 2015). However, it is currently unknown whether progesterone stimulates OPC differentiation directly and/or indirectly by the regulation of astrocytes, neurons and microglial cells. Indeed, PR has been detected in the spinal cord not only in neurons but also in glial cells (Labombarda et al., 2000).

Regarding direct progesterone actions on the oligodendrocyte linage, PR expression in oligodendrocytes remains to be clarified. Several reports have determined the expression of PR in oligodendrocyte cultures and in the white matter of the spinal cord by immunohistochemistry (Jung-Testas et al., 1991; Labombarda et al., 2000). However, these publications do not demonstrate exactly in which type of cell PR is expressed, since a double labeling experiment with an antibody against PR and antibody against a cell-specific marker of oligodendrocyte linage has not been performed (Jung-Testas et al., 1991; Labombarda et al., 2000). Concerning progesterone effects *in vitro*, the steroid is synthetized by OPC during the differentiation program in neurosphere-derived cultures (Gago et al., 2001) and increases the number of MBP-positive oligodendrocytes in mixed glial cell cultures (Schumacher et al., 2012). However, the intervention of other glial cells should not be ruled out since both cultures are not extremely pure and contain a small percentage of astrocytes (Gago et al., 2001). Experiments showing PR expression in OPC should be performed in the future since there are no reports in the literature that demonstrate it convincingly.

Astroglial and microglial cells regulate adult OPC differentiation in several pathological situations. In this regard, after lesions to the spinal cord, astrocytes and microglia cells react and produce proinflammatory mediators, oxygen free radicals and neurotoxic levels of nitric oxide (Sofroniew, 2009; Zhou et al., 2014). These proinflammatory mediators produce a feed-forward mechanism that propagates secondary injury and inflammation. Neuroinflammation contributes to white matter demyelination, oligodendrocyte loss and lack of OPC differentiation reported in SCI (Bracchi-Ricard et al., 2013). In mixed glial cultures, activated microglial cells release TNF-α which induces the apoptosis of OPC *via* the TNFR1 expressed in these cells. The same authors describe that astrocytes participate in promoting TNF-α toxicity to OPC in a contact-dependent manner (Kim et al., 2011).

Recent evidence has shown that progesterone decreases the number of astrocytes and microglial cells after SCI (Labombarda et al., 2011, 2015). Moreover, the steroid down-regulates the mRNA expression of interleukin-1β, tumor necrosis factor α, interleukin-6, inducible nitric oxide synthase, cyclooxygenase-2 (Labombarda et al., 2015) and increases the expression of transforming growth factor β, an anti-inflammatory and potent OPC differentiating factor (Palazuelos et al., 2014; Jure et al., 2019). Noteworthy, progesterone increases the number of transforming growth factorβ-expressing astrocytes and microglial cells (Jure et al., 2019). Based on the fact that anti-inflammatory microglial cells drive OPC differentiation (Miron and Franklin, 2014) the change of microglia phenotype caused by progesterone could create a pro-differentiating environment for OPC. These results are in agreement with another report which indicates that progesterone therapy induces a switch in microglia phenotype from pro-inflammatory to anti-inflammatory and suppresses NLRP3 inflammasome in cuprizone-induced demyelination mice (Aryanpour et al., 2017). These immunomodulatory effects evoke progesterone actions during pregnancy, in which a change occurs from the Th1 pro-inflammatory to a Th2 anti-inflammatory response (De Leon-Nava et al., 2009; Szekeres-Bartho et al., 2009). Other publications have supported these findings showing that progesterone has anti-inflammatory effects along with the aforementioned remyelinating actions in different animal models such as EAE (Yates et al., 2010; Garay et al., 2012) and chemical-induced demyelination ones (El-Etr et al., 2015). **Table 1** compiles the action of progesterone on neuroinflammation.

In accordance with the promyelinating actions, progesterone anti-inflammatory effects also depend on PR. It has been recently published, that PR *via* NF-κB downregulates the expression of interleukin-1β, tumor necrosis factorα and interleukin-6 mRNA after SCI (Labombarda et al., 2015). The modulation of astrocytes and microglial cells also requires PR, since their number remains elevated after progesterone treatment in spinal cord injured PRKO mice (Labombarda et al., 2015). Interestingly, PR is not expressed in surveillance microglial cells (Sierra et al., 2008). Thus, progesterone effects on microglial cells might be due to astrocyte and neuron modulation. Since progesterone stimulates growth factor production *via* PR-signaling in astrocytes, these cells become an interesting target of progesterone (Lacroix-Fralish et al., 2006; Chesik and De Keyser, 2010). On the other hand, neurons could also be involved in progesterone actions because they express PR (Labombarda et al., 2000). However, after SCI the level of PR expression is downregulated in motoneurons (Labombarda et al., 2003). One more interesting possibility is that microglial cells up-regulate PR expression after CNS injury or other demyelinating diseases. This alternative

should be explored in future experiments. Since peripheral macrophages express PR and progesterone modulates their function *via* a PR-dependent mechanism (Khan et al., 2005; Jones et al., 2008) another possibility arises. Progesterone could exert anti-inflammatory actions by inhibiting the infiltrated macrophages which invade the tissue after SCI, EAE induction and chemical-demyelination (Garay et al., 2012; El-Etr et al., 2015; Labombarda et al., 2015). In the case of lysolecithin-induced demyelination in cerebellar organotypic cultures, the perivascular macrophages could invade the tissue and mediate progesterone actions (Hussain et al., 2011).

Based on experimental evidence, progesterone effects on neuroinflammation and oligodendrocyte linage involve a PR-dependent mechanism (Ghoumari et al., 2003, 2005; Hussain et al., 2011; El-Etr et al., 2015; Labombarda et al., 2015). However, the involvement of other progesterone signaling mechanisms cannot be totally excluded. In fact, progesterone interacts with several G-couple- membrane receptors and the PR membrane component 1 (**Figure 1**). In addition, as already mentioned, progesterone is reduced to THP ($GABA_A$ modulator), which enhances the proliferation of oligodendrocyte pre-progenitors (Gago et al., 2004) and MBP synthesis (Ghoumari et al., 2003) (**Figure 1**).

Progesterone could exert myelinating and remyelinating effects by two possible mechanisms. On the one hand, it acts directly on the oligodendrocyte linage (if PR expression is definitely confirmed). Further experiments *in vitro* with extremely pure OPC cultures are needed to confirm this possibility. On the other hand, it acts indirectly *via* the inhibition of neuroinflammation by modulation of astroctyes, neurons and probably infiltrated macrophages.

Conclusion

Progesterone and THP seem to be good candidates to treat demyelinating diseases as both steroids enhance remyelination. Whether progesterone pro-myelinating effects are acting directly on oligodendrocyte linage or only mediated by the regulation of the neuroinflammatory process still remains unclear. Concerning the mechanism of action, how it is possible that progesterone antinflammatory actions are mediated by PR when microglial cells do not express this receptor. On the other hand, OPC and challenged microglial express the mPRα receptor (Labombarda et al., 2010). This non-canonical PR may also play a role in myelinating cells and neuroinflammation. However, how PR and the $GABA_A$ receptor interaction contribute to OPC differentiation and myelin synthesis is still unknown. The downstream pathways of both receptors might cross talk to each other and regulate oligodendrogenesis. THP *via* $GABA_A$ receptor could contribute to the early differentiation of OPP, when $GABA_A$ receptor activates Ca^{2+}-dependent kinases (Brinton, 2013), while progesterone *via* PR might enhance late differentiation. Further experiments should be performed to elucidate these assumptions. Lastly, it needs to be established if progesterone mechanisms of action in myelination are different from those involved in remyelination? Elucidation of multiple progesterone mechanisms remains an exciting challenge. During the last few years more groups have studied the effects of progesterone on myelination, remyelination and neuroinflammation. In the future new data related to progesterone effects on oligodendrogenesis is expected, designing novel therapeutic strategies based on progesterone pro-myelinating actions for treating demyelinating diseases.

Author contributions: *All authors wrote the manuscript and approved the final manuscript.*
Conflicts of interest: *We declare no conflicts of interest.*
Financial support: *None.*

Peer review: *Externally peer reviewed.*

Open peer reviewer: *Una FitzGerald, National University of Ireland Galway, Ireland.*
Additional file: *Open peer review report 1.*

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P-Reviewer: FitzGerald U; C-Editors: Zhao M, Li JY; T-Editor: Jia Y