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Oligodendrocyte Development and Myelination in Neurodevelopment: Molecular Mechanisms in Health and Disease

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Abstract: Oligodendrocytes are the myelinating cells of the central nervous system that constitute about 5 to 10% of the total glial population. These cells are responsible for myelin sheath production, which is essential not only for the rapid and efficient conduction of the electrical impulses along the axons, but also for preserving axonal integrity. Oligodendrocytes arise from oligodendrocyte progenitor cells that proliferate and differentiate just before and after birth, under a highly-regulated program. Both oligodendrocytes and their precursors are very susceptible to injury by several mechanisms, including excitotoxic damage, oxidative stress and inflammatory events. In this review, we will cover not only several important aspects of oligodendrocyte development and regulatory mechanisms involved in this process, but also some of the most important pathways of injury associated to oligodendrogenesis. In particular, we will also address some neurological disorders along life journey that present impairment in oligodendrocyte function and in myelination during neurodevelopment, such as periventricular leukomalacia, hypoxia/ischemia and hyperbilirubinemia that in turn can potentiate the emergence of neurological and neurodegenerative diseases like schizophrenia, multiple sclerosis and Alzheimer disease.

Keywords: Alzheimer disease, hyperbilirubinemia, hypoxia/ischemia, multiple sclerosis, oligodendrocyte development and myelination regulation, oligodendrocyte injury, periventricular leukomalacia, schizophrenia.

1. INTRODUCTION

Mammalian myelination occurs as a multi-step process involving: (1) oligodendrocyte precursor cell (OPC) proliferation, (2) OPC migration, recognition and adhesion to the appropriate axon, (3) synthesis and transport of myelin components to the oligodendrocyte (OL) outer membrane, (4) wrapping of the myelin membrane around the axons and (5) compaction of the myelin sheath (for review see [1]). OL differentiation and maturation occur in an extremely elaborated and defined program that involves both intracellular and extracellular factors, with distinct roles at each step. These mechanisms will allow the exact timing of OPC differentiation and control the proper recognition of the axon to be myelinated. Here, we first address the current knowledge on temporal OL lineage progression and determination of myelination, highlighting oligodendrogenesis in humans vs. rodents.

The last weeks of gestation and the first postnatal months are crucial periods for white matter maturation, which render to this period an increased vulnerability to any kind of insult. Several cellular and molecular mechanisms have been implicated in preoligodendrocyte injury and death [2], resulting in impaired myelination. Here we will review how excitotoxicity, oxidative/nitrosative injury by free radicals, microglial activation and consequent inflammatory response may contribute to OL damage and delayed/deficient myelination.

Major white matter damage is usually associated with injury in premature infants while pathological conditions affecting term neonates mostly reduce neuronal survival. Nevertheless, diffuse white matter injury may also be observed upon some neonatal harmful conditions. White matter injury is one of the most common cerebral neuropathologies observed in very premature infants (<30 weeks of gestational age) and termed as periventricular leukomalacia (PVL) [3]. Other perinatal co-morbidities including intrauterine infection, cerebral hypoxia-ischemia (HI) injury, and, as recently reported, moderate to severe hyperbilirubinemia [4] are known determinants of marked white matter damage in preterm babies. These conditions may result in severe cognitive deficits detected during child infancy as cerebral palsy [3, 5], or in subtle changes that are only diagnosed in early adulthood such as schizophrenia [6], or even been associated to the emergence of neurodegenerative disorders such as multiple sclerosis or Alzheimer's disease. So, we will discuss how OL function is impaired during these neurodevelopment-associated conditions and what long-term sequelae may be associated.

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2. OLIGODENDROCYTES DURING CENTRAL NERVOUS SYSTEM MYELINATION

2.1. Oligodendrocyte Origin

OL development is better understood in the spinal cord (SC) than in the brain. The human OL lineage has been characterized in the SC mainly during the first trimester and in the human cerebrum for the second and third trimesters.

Since OL are evenly distributed throughout the adult central nervous system (CNS), it would be reasonable to suppose that they are produced from all regions of the neuroepithelium. However, several studies demonstrated that, in both SC and telencephalon, OL originate from specific regions. A critical step during this process is the establishment of distinct progenitor cell domains [7, 8]. Embryonic oligodendroglial specification shares mechanistic features with motor neurons (MN) of the ventral neural tube [9, 10]. In the SC, most OL derive from a specialized domain of the ventricular zone, called MN precursors (pMN) domain, which gives rise to MN precursors and then to oligodendrocyte precursor cells (OPC) [11, 12]. pMN progenitors develop in stages, after the beginning of MN formation, that is completed at embryonic day (E) 10.5 in mice; a phase of OL production starts at E12.5. This process depends on Sonic hedgehog homolog (Shh) signalling [13] that acts

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through activation of Olig2, a transcription factor essential for OL development [11].

Interestingly, it seems that during early foetal stage OL develop only from ventrally derived progenitor cells as demonstrated when E14 rat SC were divided into dorsal and ventral regions and the cells cultured separately, OL develop only in ventral cultures [14, 15]. OPC derived from the pMN domain continue to proliferate after specification and migrate both laterally and dorsally to occupy all areas of the SC. At a later foetal phase (starting around E15.5), an additional source of OPC arises in the dorsal SC, contributing to 10-15% of the final OL population in the SC [16, 17].

In the forebrain, the formation of OL is a process even more complex, with multiple waves of OPC production and migration from embryonic to postnatal stages that emerge in a ventral-to-dorsal progression [18]. At E12.5, the first wave of OPC develops from Nkx2.1-expressing precursors in the ventricular zone of the ventral medial ganglionic eminence and anterior entopeduncular areas [19, 20]. Subsequently they migrate to all parts of the telencephalon, entering the cerebral cortex at E16. A second wave of OPC from Gsh2 expressing precursors occurs around E14.5 from the lateral and/or caudal ganglionic eminences. Finally, a third wave within the postnatal cortex from Emx1-expressing cortical precursors starts around birth at postnatal (P) day 0 [18]. After this process, OPC exhibit multidirectional migration in the ventricular zone to distant sites under control of several repulsive and attractive cues [21, 22]. Recent studies suggest that different waves of OPC can myelinate distinct regions of the brain, indicating that different functional subpopulations of OPC may have distinct functions [23]. Moreover, besides OPC density does not perceptibly vary during adulthood, it is higher in white matter than in grey matter [24, 25]. This could be in part explained by the higher rate of OPC proliferation in the white matter, since these OPC are in a proliferative state and contribute to adult oligodendrogenesis, while grey matter OPC are quiescent or slowly proliferative and most remain in an immature state [24].

2.2. Temporal Oligodendrocyte Lineage Progression

The proliferation and migration of neurons occurs mainly during the prenatal period, while in glial cells are essentially postnatal processes that last for an extended period after birth, with differentiation and maturation taking place throughout childhood. Given these overlapping situations several questions concerning the temporal extent of each glial cell lineage progression during the postnatal period in humans, as well as their intermixed phases still remain unknown.

OL progression along several differentiation steps can be identifiable according to their proliferative and migratory capacities, morphological changes and the expression pattern of specific markers. In this context, several studies identified four different stages of OL differentiation, namely: OPC, preoligodendrocytes (pre-OL) or late OPC, immature or pre-myelinating OL and mature or myelinating OL. OPC have a high proliferative and migratory capacity and express specific markers like platelet-derived growth factor receptor α (PDGF-Rα), ganglioside A2B5, proteoglycan NG2 [26, 27], polysialic acid-neural cell adhesion molecule [28] and fatty-acid-binding protein (FABP)7 [29]. The majority of authors have described OPC as cells with small polygonal soma and bipolar morphology characteristic of neural precursor cells, with only few processes that are short in length and emanate from the opposing poles of the cell body [30]. However, some studies showed that NG2 progenitors evidence slightly different morphologies depending on their location in the brain [31, 32]. During progression along oligodendroglial lineage, OPC differentiate into pre-OL that acquire a multipolar morphology with short processes and start to express OPC markers as well as the sulfatide recognized by the O4 antibody [33] and the gadd-related protein (GRP) 17 [34], which persist until the immature OL stage. After losing the expression of NG2 markers, the immature OL present long ramified branches and start the expression of other specific markers like galactocerebroside C (GalC) [35, 36]. For the initial step of myelin formation, immature post-mitotic OLs need to extend several cytoplasmic protrusions (filopodia) in order to find suitable myelin-competent axons. Finally, mature OL synthesize the major myelin structural proteins in an orderly manner, i.e. myelin basic protein (MBP), proteolipid protein (PLP), myelin associated glycoprotein (MAG) and myelin OL glycoprotein (MOG) and to extend membranes that form compact enwrapping myelin sheaths around the axons [37-39]. Mature OL express markers such as myelin gene regulatory factor (MRF)/gene model 98 [40], zinc finger protein 488 [41] and FABP5 [29].

In humans, only a few studies addressed the temporal OL development and also described the existence of four stages of OL maturation between 10 and 41 gestational weeks (g.w.): OPC, pre-OL, immature OL and mature OL. As observed in animal models, the first OL observed in humans are OPC that reside in the forebrain at 10 g. w.. OPC appear in more relevant numbers only around 15 g.w., when they appear in higher numbers in the ganglionic eminences and in the cortical ventricular zone/subventricular zone [42]. Later, between 18 and 28 g.w., some immature OL are identified but OPC and pre-OL are yet the most predominant cells from OL lineage. Between 28 and 40 g.w. is described a high degree of OL differentiation, with a consequent increase in the number of immature OL and the appearance of some mature OL that are restricted to the periventricular white matter [43, 44]. Approximately at the 30 g.w. a marked increase in O4+ cells displaying a complex multipolar morphology is observed mostly in deeper and milder cerebral white matter, while they are sparingly distributed in the superficial white matter, and not detected in cerebral cortex. Overall, the first MBP+ cells are observed between 20 and 28 g.w. in subcortical regions, but are only broadly visualized between 36 and 40 g.w., with an increase from 1 to 5% in total brain volume that contains myelinated white matter [43, 45].

In rodents, the first OPC are observed in the telencephalon, namely in the entopeduncular area, around E9.5 [46]. Moreover, another study showed that ventral telencephalic regions have a greater capacity to generate OL *in vitro* than the corresponding cortical regions in E13 rat brain [47]. Later, at P2, both rat and mouse present an high proportion of pre-OL in the cerebral white matter together with a minor number of immature OL are a minor population. In contrast, the white matter contains more than 80% of immature OL at P7 that begin to myelinate axons [48].

In comparison, OL lineage progression in the P2 rodents (Fig. **1**) is similar to that of humans between 18 and 27 g.w. in cerebral white matter, being mostly composed by pre-OL and few immature OL. At P7, rodent white matter presents a maturation state similar to the one observed in human between 30 and 36 g.w. [49]. Finally, the first MBP+ cells are only observed around P7 in rodents, increasing abundantly at P14, both in the rat and mouse brain [50-52], what is approximate to the extent of myelination in many full-term infants [53].

3. REGULATION OF OLIGODENDROCYTE DEVELOPMENT AND MYELINATION

OL development is orchestrated by an extremely complex program that involves several factors with distinct roles at each step. These signals serve two major purposes: 1) help to control the proper timing of OPC differentiation to ensure myelination at the appropriate moment and place, and 2) control and match the number of OL to the axonal surface area requiring myelination. Several intracellular and extracellular molecules modulate the fate of OL in the myelination process as discussed below.

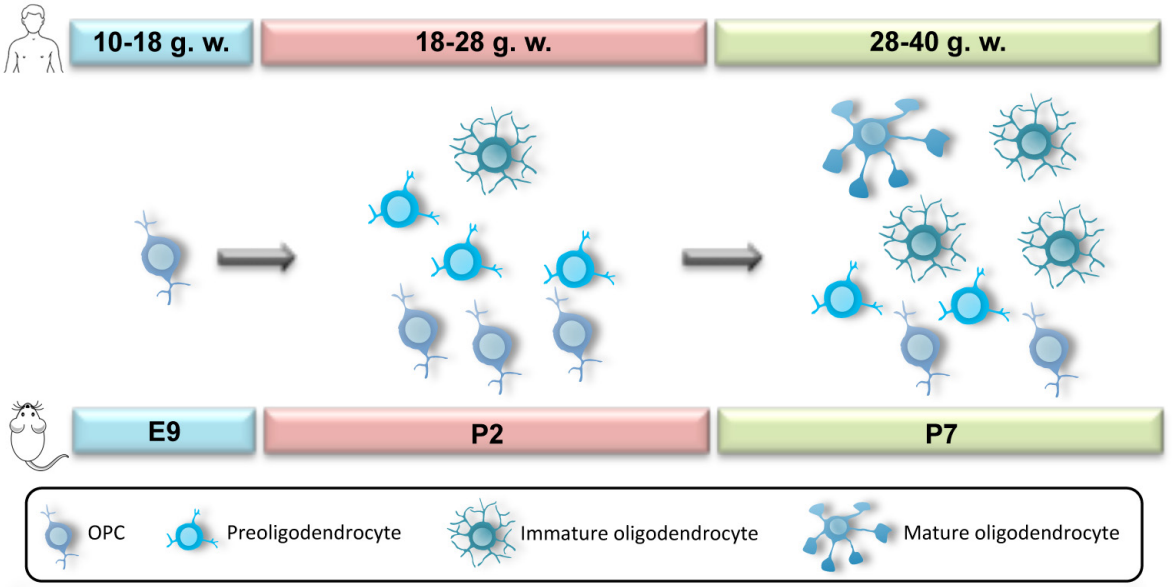

Fig. (1). Oligodendrocyte lineage development in rodents and humans. Oligodendrocyte precursor cells (OPC, with NG2 positive staining) arise around embryonic (E) day 9 in rodents and between 10 and 18 gestational weeks (g.w.) in humans. Lately, at postnatal (P) day 2 and between 18 and 28 g.w., the proportion of cells along oligodendrocyte (OL) lineage is very similar being composed mainly by OPC and pre-OL (more ramified but also positive to NG2 staining), with a minor population of immature OL (O4+ staining). White matter at P7 rodents is comparable to that observed in humans between 28 and 40 g.w., with predominance of immature oligodendrocytes and a progressive increase in mature oligodendrocytes that express the myelin basic protein.

3.1. Transcription Factors

Many transcription factors have been implicated in myelination, from lineage specification through OL progressive stages of maturation until the myelination process. The most studied transcription factors are two families including: Sox group (Sox8, Sox9 and Sox10) and Olig genes (Olig1 and Olig2) [54]. Regarding to Sox family, Sox9 is involved in OL specification, while Sox 8 is required for the terminal differentiation and Sox10 is necessary for the development of myelin-forming OL [55, 56]. The two Olig genes besides structurally similar and co-ordinately expressed, encode proteins with quite distinct biological capabilities. Expression of Olig2 plays prominent roles in multipotent neural progenitor cells of the embryo and adult being necessary for OL lineage development. Indeed, Olig2 is required for the development of NG2+ progenitor cells [11, 57]. Interestingly, Olig2 is strongly upregulated during acute brain damage [58], what may indicate an increase in OL proliferation to counteract defects in the number of OL and myelination. On the other hand, Olig1 appears to be mostly implicated in OL maturation, although there is disagreement on whether there is an absolute requirement of Olig1 during normal development. Some studies demonstrated that Olig1 is involved in the final stages of myelin production [11, 59] and in regeneration [60]. *In vivo*, *Olig1* null mice showed that loss of Olig1 causes a transient delay in the appearance of differentiated OL and myelination without long-term myelin deficits [11, 61]. However, a different study in other *Olig1* null mice found severe myelination defects that led to early postnatal lethality [62].

3.2. Cytoskeleton Components and their Regulation

As described before, OL suffer continuous remodelling of the cytoskeleton in order to be able to extend their processes and unsheath the axons. Changes in OL shape are in part mediated by the cytoskeleton that is composed by microtubules (MT) and microfilaments (MF). These elements have distinct roles; while MT confer mechanical stability to OL processes, MF mediate process outgrowth and basic stability, as a consequence of their localization immediately beneath the plasma membrane.

MT are composed by heterodimers of α- and β-tubulin protein subunits that are anchored in the MT organizing centre in the vicinity of the nucleus and extending to the OL periphery, giving origin to filaments arranged in parallel to the main axis of the processes [63, 64]. More recently, the importance of cytoskeleton during OL development was emphasized by the discovery of a specific form of β-tubulin, the βIV-tubulin that has not yet been found in other CNS cells [65]. Tubulin undergoes several posttranslational modifications, including α-tubulin acetylation that is correlated with higher stability in more mature OL [66]. Indeed, to increase MT dynamics during OL maturation and myelination, tubulin must be deacetylated in a process mediated by silent information regulator type (SIRT) 2 [67].

Actin, MF-associated protein, is present in OL in two different states, as globular monomers (G-actin) or as filamentous polymers (F-actin). *De novo* actin nucleation to form G-actin is a kinetically unfavourable process due to the extreme instability of these small action oligomers, but it is thought that both actin-related protein 2/3 (Arp2/3) complex and formins could be involved as stabilizers [68]. It is known that Arp2/3 complex is activated by cortactin and by Wiskott-Aldrich syndrome protein (WASP) family proteins [69]. These proteins polymerize actin monomers into F-actin filaments to generate small membrane protrusions for filopodia and lamellipodia formation [70, 71]. Filopodia are narrow structures supported by tightly packed parallel actin bundles with their plus ends facing the membrane, whereas lamellipodia are broader and contain actin networks arranged in an approximately orthogonal manner [72, 73]. WASP proteins are themselves controlled by Rho GTPases that regulate cytoskeletal structure by mediating actin polymerization [74, 75]. Rho GTPases are divided in 8 subfamilies that include the RhoA-related subfamily (RhoA, RhoB, RhoC), the Rac1-related subfamily (Rac1, Rac2, Rac3, RhoG) and the Cdc42-related subfamily (Cdc42, TC10, TCL, Chp/Wrch-2, Wrch-1). Rho GTPases act as binary molecular switches that cycle between an inactive guanosine diphosphate (GDP)-bound and an active guanosine triphosphate (GTP)-bound state in response to extracellular stimuli. In the CNS, active Rac1 and Cdc42 act as positive regulators of morphological differentiation, inducing process extension and

branching, while RhoA acts as a negative regulator inhibiting process elongation [76]. RhoA, B and C activate the immediate downstream Rho-associated protein kinase (ROCK), which in turn phosphorylates a number of actin cytoskeleton regulators, like the enzyme myosin light chain phosphatase and the myosin light chain [77]. This direct phosphorylation increases the contraction of the actomyosin network [78, 79]. So, ROCK inhibition in OPC results in a significant generation of branches and cell processes in early differentiation stages, followed by accelerated production of MBP [80]. Rac1 and Cdc42 activate WASP family of proteins, like neuronal WASP (N-WASP) and Wiskott-Aldrich syndrome protein family verprolin homologs (WAVE) 1/2 [81, 82]. These proteins, as already mentioned, bind the Arp2/3 complex and alter its conformation for actin binding. WAVE1 and N-WASP are also critical for myelination, since deletion of WAVE1 in mice triggers hypomyelination, while the N-WASP inhibitor wiskostatin causes retraction of filopodia and lamellipodia and impairs myelination [83].

3.3. Extracellular Factors

Many studies point out the importance of extracellular factors released by neurons and glial cells in oligodendrogenesis.

3.3.1. Growth Factors

Several lines of evidence have demonstrated the importance of growth factors in OL development; while some promote the maintenance of the OPC pool, others induce OPC differentiation into myelinating OL. Moreover, one mechanism that may determine the final number of OL is the competition for limiting amounts of factors, like platelet-derived growth factor A (PDGF-α), fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 (IGF-1), neurotrofin 3 (NT-3) and ciliary neurotrophic factor (CNTF) [84-86]. PDGF-α is a potent mitogen produced by both astrocytes and neurons that regulates the proliferation and survival of OPC, preventing premature differentiation [87-89] and inducing early OPC to proliferate for an indefinite number of divisions *in vitro* [90]. In addition, it is also known that NG2+ cells in white matter exhibit greater proliferative response to PDGF-α than those in the grey matter [91], revealing regional responses in PDGF-induced proliferation. FGF-2 is a mitogen that stimulates proliferation of early and late progenitors, maintaining the expression of the PDGFRα and blocking the differentiation into OL [92, 93]. In addition, FGF-2 induces withdrawal of myelin sheets and downregulation of the major myelin proteins, at both the protein and mRNA levels [94, 95]. Although PDGF-α or FGF-2 act individually with different effects on OPC, if together they induce continuous proliferation and produce a "conditional immortalization" of OPC [96]. IGF-1 in combination with FGF-2 and PDGF-α synergistically promotes DNA synthesis in OPC [97] and *in vitro* proliferation [98]. Recently, another FGF, the FGF-8, was shown to induce proliferation and migration of postnatal mouse OPC, as well as differentiation into mature OL [99]. A different study has shown that OPC cultured in the presence of FGF-8 expressed more MBP compared to FGF-2 and in OL cultures. While FGF-2 downregulated mature OL markers and induced a reverted state, such effects were not observed with FGF-8, revealing a distinct action of these two similar growth factors [100]. In what concerns NT-3, it induces OPC proliferation *in vivo* [101, 102], but presents a weak mitogenic effect *in vitro* [103].

Thyroid hormone (T3) is one of the best-characterized differentiation factors. This growth factor blocks OPC proliferation *in vitro* and induces their differentiation into OL even in the presence of PDGF-α [84, 104]. T3 is necessary for proper myelination timing and production of normal levels of myelin *in vivo* and *in vitro* [105-107]. Moreover, while increased concentrations of T3 as those observed in hyperthyroidism accelerate myelination, hypothyroidism results in its decrease [108]. However, it seems that this hormone is not essential for OL differentiation, but may be involved in regulating the moment of differentiation, since OPC cultured in the absence of mitogens stop dividing and differentiate rapidly, even in the absence of T3 [84]. However, in the presence of mitogens, T3 signalling is necessary to promote the complete differentiation of OPC [109]. A recent study have also demonstrated that GC-1, a thyromimetic compound with selective thyroid receptor β activity, promotes oligodendrogenesis from both rodent and human OPC and increases the production of MBP, cyclic nucleotide 3'-phosphodiesterase (CNP) and MAG [110]. Moreover, it has been proposed that T3 is necessary early in OL development for apotransferrin expression and action, which in turn will favour OL maturation and myelination [111].

Besides the positive cues that promote OPC proliferation, migration and differentiation, there are inhibitory factors that also regulate OL development, such as bone morphogenetic proteins (BMP) secreted by astrocytes [112, 113] that inhibit OPC differentiation into myelinating OL [114, 115].

3.3.2. Cytokines and Chemokines

Cytokines are pleiotropic factors and most of them are secreted proteins or glycoproteins, while chemokines are small molecular weight cytokines specialized in causing cell movement. However, both use chemical signals to induce changes in other cells. Cytokines and their receptors are expressed physiologically in CNS cells and are important in the development and function of the brain. Some cytokines involved in OL development are interferon (IFN)-γ, interleukin (IL)-1β, transforming growth factor (TGF)-β, IL-6 and leukemia inhibitory factor (LIF). Both IL-1β and TGF-β are able to inhibit OPC proliferation and enhance their differentiation [116-119]. On the contrary, IFN-γ has exactly the opposite effect in OL development, inhibiting OPC differentiation and the cell cycle exit [120, 121]. Exogenous LIF can stimulate OPC proliferation [122], differentiation [116] and myelination [123]. Moreover, selective activation of TNF receptor 2 (TNFR2) on astrocytes leads to enhanced LIF gene expression and secretion, which then stimulates the differentiation of co-cultured OPC into MBP+ mature OL [124]. After TGF-β gain of function, enhanced OPC cell cycle exit accelerates oligodendrogenesis and subcortical white matter myelination, while TGF-β receptor II deletion in OPC prevents their maturation into mature myelinating OL, leading to hypomyelination in the developing subcortical white matter in mice [125]. Recently, IL-17A has also been described as regulator of OL development, since OPC stimulated with IL-17A exit the cell cycle and differentiate with an increased expression of PLP [126].

There is little evidence that OL produce chemokines, but it is known that in cell cultures CXC chemokines, such as growth-related oncogene-α, IL-8 and stromal cell-derived factor-1α stimulate MBP production [127], while astrocytic CXC ligand 1 in the SC enhances the proliferative response of OPC to PDGF-α [128]. It was also demonstrated that CXCL1-mediated signalling on OPC inhibit their migration and induce proliferation by a PDGF-α-driven mechanism [21].

3.4. Neuron-Oligodendrocyte Communication

Since most of the factors described above are also produced by astrocytes the role of neurons on myelination was not initially apparent. To note, however, that neurons can direct the myelination of their axons, and consequently the OL differentiation, through neuronal-OL cross talk. It was initially thought that axon diameter represented the only and crucial regulator of myelination [129], with OL selecting axons with diameters above 0.2 μm and excluding dendrites (Fig. **2A**) [130]. A recent study using optogenetic stimulation of the premotor cortex demonstrated that neuronal activity induces oligodendrogenesis and myelination within the deep layers of the premotor cortex and subcortical white matter [131]. However, the molecular cues for this recognition remain unclear. It seems that besides axon diameter and neuronal activity, also neurotransmission and cell adhesion molecules play an important role in OL differentiation and myelination.

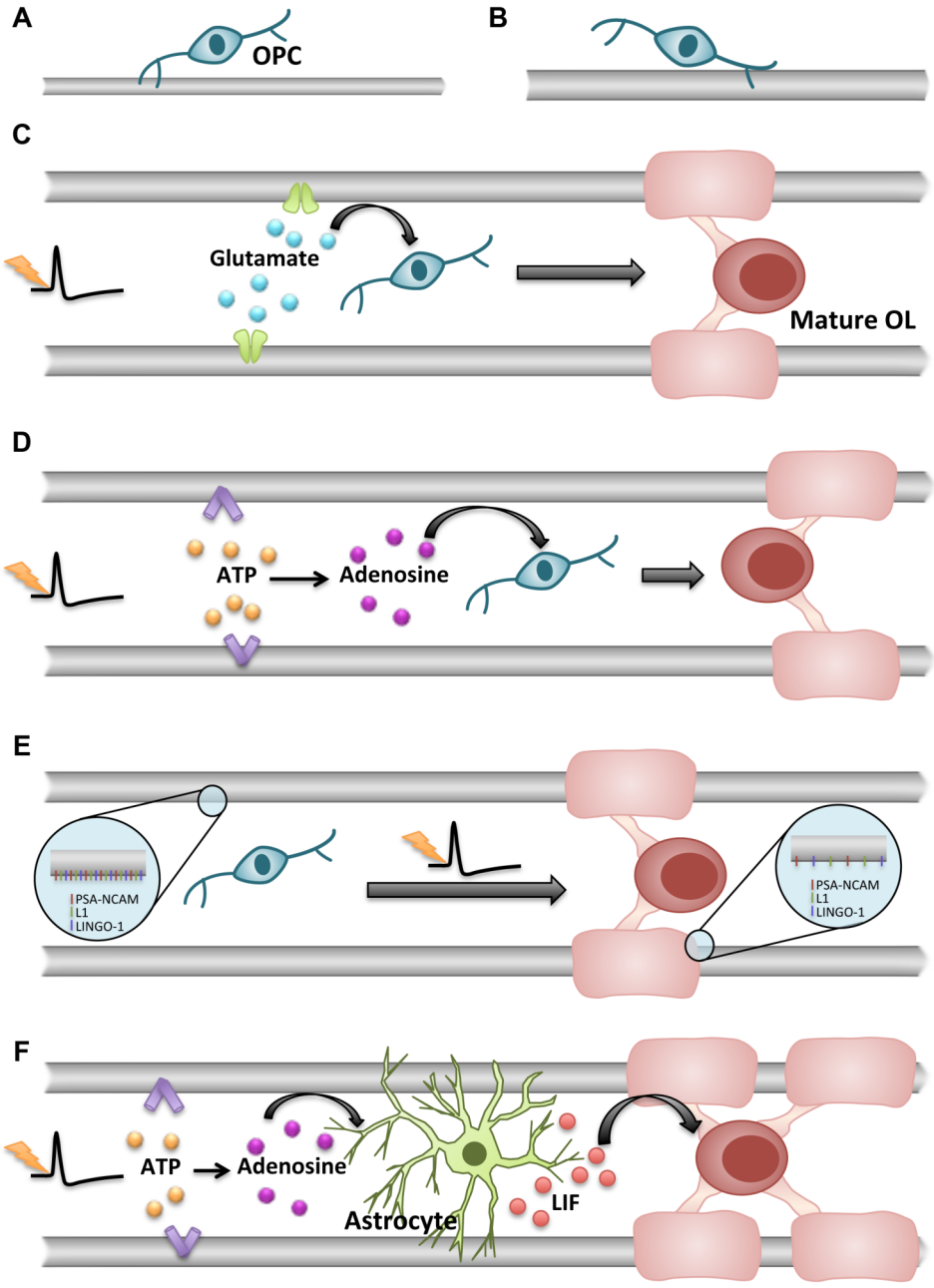

Fig. (2). Oligodendrocyte development and myelination are regulated by neuronal signals. **A**) Oligodendrocytes (OL) do not myelinate axons with diameters ~~above~~ 0.2 µm and dendrites. **B**) In absence of electrical activity oligodendrocyte precursor cells (OPC) do not differentiate and are not able to myelinate. **C**) Electrical activity leads to release of neurotransmitters by neurons like glutamate that ~~includes~~ OL maturation and myelination. D) Electrical activity leads to adenosine triphosphate (ATP) release from axons, which in turn generates adenosine that induces OL maturation and myelination. **E**) Electrical activity alters the expression of cell adhesion molecules on the axons, like polysialic acid-neural cell adhesion molecule (PSA-NCAM), L1 and leucine-rich repeat- and Ig domain-containing nogo receptor-interacting protein (LINGO)-1, that are involved in cell-cell interactions and consequently in myelination onset. F) After OPC differentiation into mature oligodendrocytes, ATP release from axons will stimulate the release of leukemia inhibitory factor (LIF) from astrocytes, which in turn will promote myelination.

3.4.1. Neurotransmitters and their Receptors

As mentioned, the production of myelinated axons requires a precise matching of the number of OL generated with the length of axons to be myelinated. So, OL at different stages of development have to express ion channels as well as purinergic and other membrane receptors in order to detect the impulse activity through the activity-dependent release of molecules from axons, such glutamate and ATP.

Both OPC and OL, express α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-Methyl-D-aspartate (NMDA) receptors for glutamate. While AMPA/kainate receptors are predominantly expressed in the cell body, particularly in immature OL, NMDA receptors are mainly present in the myelinating processes [132-134]. It was reported that OL AMPA receptors lack GluR2 subunit and therefore are Ca^{2+}-permeable, which has a crucial relevance for the damaging actions of glutamate on

OL [135]. However, it is not clear how glutamate signalling induces changes in OL maturation. Studies performed in *in vitro* cultures showed that glutamate response is more pronounced in OPC and immature OL than in mature OL (Fig. **2C**) [136, 137]. Furthermore, it seems that glutamate-evoked current do not generate different responses in OPC and mature OL [138]. Studies with cells in culture and organotypic slices demonstrated that activation of AMPA/kainate inhibits PDGF-induced proliferation and promotes OPC differentiation [139, 140]. NMDA receptor preferential location in the distal process of OL suggests that it may have a role in controlling axon-OL interactions [139]. More recently, activation of NMDA receptors in OPC derived from subventricular zone multipontent cells was shown to increase their differentiation and myelination rate *in vitro* [141]. It is now established that NMDA activates PKC/NADPH oxidase/p67 signalling, which in turn generates intracellular reactive oxygen species (ROS) that in parallel can set off PI3K/mTOR and/or ERK pathways to induce OL differentiation [142]. However, contradictory data have demonstrated that NMDA receptors play no role in OL differentiation and myelination [143, 144]. A recent study showed that there are two distinct modes of OL myelination: one independent of neuronal activity and other dependent on action potentials. It was demonstrated that neuregulin switches OL between these two myelination programmes by increasing NMDA receptor-mediated currents in OL, making them more sensitive to glutamate released from active neurons and consequently increasing myelination due to accelerated glutamatergic signalling [145].

OL in different stages of maturation also express ATP-gated P_{2x7} receptors that are permeable to Ca^{2+}. Whereas glutamate has been mostly shown to regulate the early development of OL, adenosine and ATP are recognized as modulators of late OL development and myelination. It is believed that ATP, released by action potential firing, does not act directly on OL. Instead, the adenosine resulting from conversion of ATP by extracellular ATPases, promotes an increase in OPC intracellular Ca^{2+}, inhibiting their proliferation and stimulating their differentiation, consequently promoting the myelin assembly (Fig. **2D**) [146]. In later development, adenosine acts indirectly by inducing astrocytes to release LIF, which in turn enhances myelination by mature OL (Fig. **2F**) [123].

Gamma-aminobutyric acid type A ($GABA_A$) receptors are expressed in OL at different maturation stages [147, 148] and GABA is known to depolarize both mature and progenitor cells. Moreover, OPC present in both grey and white matter receive GABAergic synaptic input from axons [149], through $GABA_A$ receptors present in OPC, inhibiting outward rectifying potassium channels [147] that can lead to a reduction in proliferation.

As described here, Ca^{2+} influx across OL plasma membrane may occur through different routes, e.g. ligand-operated channels, such as ATP-gated P_{2x7} and glutamate receptors and voltage-operated Ca^{2+} channels (VOCC). Several studies have addressed the importance of Ca^{2+} signalling in OPC differentiation and myelination [150], as well as for process extension and OPC migration [64, 151]. VOCC regulate the extension/retraction of OPC processes [152] through an increase of the amplitude of spontaneous Ca^{2+} oscillations in the soma and in the front process of migrating OPC leading to an accelerated cell migration by promoting Ca^{2+} dependent soma translocation and front processes formation [153]. Moreover, activation of VOCC by plasma membrane depolarization increases OPC morphological differentiation, expression of mature OL markers and myelination [154].

Nitric oxide (NO), in the CNS, is generated largely by the neuronal subtype of NO synthase (nNOS) in response to a rise in intracellular Ca^{2+}. OL are also a target of physiological NO and *in vitro* OL responded to low NO concentrations with a striking increase in arborisation, revealing that NO can contribute to the maturation of OL [155].

3.4.2. Cell Adhesion Molecules

Other candidates for axonal signalling to OL that regulate myelination are the cell adhesion molecules. These molecules have the ability to bring the axon and glial cell into close apposition and to transduce the signals between such cells [156]. The best-studied adhesion molecules are the polysialic acid-neural cell adhesion molecule (PSA-NCAM), L1 cell adhesion molecule and leucine-rich repeat- and Ig domain-containing nogo receptor-interacting protein 1 (LINGO-1) (Fig. **2E**). During development, the haemophilic NCAM-NCAM adhesion, i.e. cell-cell interaction, is prevented because all growing nerve fibres in the CNS express the PSA-NCAM [157], persisting in areas of adult brain that exhibit plasticity [158-160]. So, in order to occur interactions between OL and neurons and consequently myelination, PSA-NCAM has to be downregulated when neurons are electrically active [161-164]. In a more recent study it was demonstrated that PSA-mediated signalling mechanism is one of the regulators of primary myelination in the human foetal brain [165].

L1, an adhesion molecule also expressed in axonal surface [166], is diffusely expressed on the non-myelinated axons, while it drastically reduces upon myelination, presenting low levels on myelinated axons [42]. However, in this case, the L1 expressed in axons promotes myelination, probably acting at the very early stage of OL/axon adhesion, through binding possibly to a specific oligodendroglial receptor not yet identified. After an initial stage of adhesion, the downregulation of L1 from the axonal surface is necessary to the myelination onset and the beginning of wrapping process [167].

LINGO-1, a transmembrane protein with leucine-rich repeats and an immunoglobulin domain expressed in both OL and neurons, interacts with Nogo-receptor, and negatively regulates OL differentiation and myelination [168]. Loss of LINGO-1 function in OL leads to increased myelination while its overexpression inhibits myelin assembly [169]. In zebrafish, the lack of LINGO-1 was shown to enhance myelination and OL differentiation during embryogenesis [170]. LINGO-1 is also able to inhibit MBP transcription by constitutive inhibition of Fyn kinase, a kinase involved in the upregulation of MBP transcription during OL maturation [169]. Although the molecular mechanism by which LINGO-1 influences membrane generation is not clear, it is known that LINGO-1 in OL inhibits process extension once it is a constitutive activator of RhoA [171]. In addition, the inhibition of LINGO-1 leads to the downregulation of RhoA activity thus promoting *in vitro* OPC differentiation [172]. Consistent with these observations, it was demonstrated that OPC differentiation can be inhibited both by intercellular signalling and activation of RhoA [173]. Furthermore, a recent study revealed a new regulatory mechanism that involves interaction between LINGO-1 and ErbB2, since LINGO-1 can directly bind to ErbB2, block ErbB2 translocation into lipid rafts and inhibit its phosphorylation for activation, thus preventing consequently OL differentiation [174].

3.4.3. Axo-Glial Contact and Node of Ranvier Formation

During the first stages of myelination, mature OL interacts with axons, resulting in the formation of an axon-glial contact, dependent on adherens junctions, between the distal uncompact loops of myelin and the axolemma that will define the paranodal region and separate the node of Ranvier (unwrapped axonal membrane) from the juxtaparanode. In this context, the differentiation of these structural and functional regions of the axonal membrane is another important factor that regulates OL differentiation and myelination.

Internodal segments alternate with nodes of Ranvier, where voltage-gated Na^+ channels are accumulated allowing the generation of the action potential during saltatory conduction [175]. The precise localization of Na^+ channels in the node is a critical process during myelination. So, to ensure the high concentration and the anchoring of these channels specific neuronal and OL proteins have

to interact, like the cytoskeletal adaptor ankyrin G (Ank-G) [176, 177], the actin-binding protein spectrin βIV [178] and cell adhesion molecules of the immunoglobulin superfamily Nrcam and neurofascin-186 [179]. The nodes and the initial segment are enriched in Ank-G that has an essential role in the formation of the node of Ranvier, since it binds not only to Na^+ channels but also to paranodal adherens junction proteins contactin 1, neurofascin 186 [180-183]. Regarding to Na^+ channels, they bind through their cytoplasmic loops with Ank-G that in turns bind to the actin cytoskeleton through spectrin βIV [176, 177, 181]. During node formation occurs a developmental switch of sodium channel isoform expression from Nav1.2 in immature nodes to Nav1.6 in mature nodes and besides the precise mechanisms that regulates this switch are still not clear, it is thought to be required for myelination [184]. It has also been described that interaction between Ank-G and contactin 1 enhances the expression of Na^+ channels, indicating that this protein might have an important role in the expression of these channels in the node [181, 185]. In other hand, contactin 1 interact with neurofascin 155 and contactin 2/Tag 1, proteins of the oligodendroglial paranodal loops to guarantee the myelin-axolemma adherens junction integrity [182].

In order to define and initiate the formation of nodes of Ranvier, interaction between cell adhesion molecules and the extracellular matrix has to occur in paranodal regions, which are present immediately in the adjacent area of nodes on both sides [182]. In the paranodes, the compact myelin membrane opens up and the cytoplasm of the OL is pushed to the edges forming cytoplasm-filled glial loops that are attached to the axolemma and wind helically around the axon. These axo-glial septate junctions appear late during myelination and comprise three major components, two cell recognition molecules, the contactin-associated protein (Caspr) [186, 187] and contactin [184] on the axonal side, and the 155-kDa isoform of Nfasc (NfascNF155) on the glial side [188]. Caspr is a transmembrane protein that is involved in cell adhesion and intercellular communication, contactin is a glycosylphosphatidylinositol (GPI)-anchored protein [189]. Caspr and contactin interaction is necessary for the correct export of Caspr from de endoplasmic reticulum (ER) to the plasma membrane [190], and regulates the glycosylation and transport of contactin [191], whereas Caspr is required to maintain contactin at the paranodes [191, 192]. It is also described that both proteins are crucial for the establishment of the axo-glial septate junction, since their absence lead to the disappearance of septa and a widening of the space between the paranodal loops and the axon [191, 193]. However, besides the role of NfascNF155 is not clear, it is known that glial-specific ablation of NfascNF155 results in loss of septate junctions and paranodal disorganization [194].

In the juxtaparanodes, regions flanking the paranode, are expressed delayed rectifier K^+ channels, including KV1.1 and KV1.2, that are thought to be responsible for the maintenance of the resting potential in the internodes and the axo-glial communication [195]. Juxtaparanodal K^+ channels are thought to act as an active damper of re-entrant excitation and to help in the maintenance of the internodal resting potential [196]. These channels co-localize and form a complex with the axonal transmembrane Caspr2 [197]. In addition, two other proteins are present in juxtapanodal regions, the transient axonal glycoprotein-1 (Tag1), a GPI-anchored cell adhesion molecule [198], and connexin (Cx29) in the glial membrane [199]. Recent studies showed that Tag1 and Caspr2 form a complex, which consists of a glial Tag1 molecule and an axonal Caspr2/Tag1 heterodimer, being that essential for the accumulation of K^+ channels in the juxtaparnodes [200, 201]. In addition, compact myelin is also needed for proper K^+ channel localization and stabilization [202].

4. MECHANISMS OF OLIGODENDROCYTE INJURY

OL have a great metabolic rate in order to myelinate properly. Some studies pointed out that during myelination peak, OL produce three times its weight in myelin per day, and support membrane up to 100 times the weight of its cell body [203, 204]. This feature turns OL into cells highly vulnerable to several pathways of damage resulting from activation of numerous intracellular mechanisms, most of them produced by extracellular factors released by other CNS cells. In this context, OL frequently respond by producing poor-quality myelin, which may contribute to the pathology observed in several neurological diseases.

4.1. Molecular Mechanisms

Among the molecular mechanisms that mediate OL damage, several authors indicate excitotoxicity, oxidative damage, ER stress and cytokine signalling as the key events.

4.1.1. Excitotoxicity

As described before, OL express several receptors such as AMPA, kainate and NMDA receptors that predispose them to excitotoxic cell death. Additionally, OL also express the ATP receptor P_{2x7} that make them vulnerable to increased levels of extracellular ATP. OL are the predominant cells for glutamate clearance in human white matter, and in this context they express the excitatory amino acid transporter (EAAT)-1 and -2 [132, 205]. In situations of ATP depletion these transporters revert their action, promoting changes in ion gradients and glutamate release from OL [135, 206], as shown in Figure **3**.

The toxicity induced by glutamate and ATP primarily depends on excessive Ca^{2+} influx (Fig. **3**), given the activation of OL NMDA receptors, consequent membrane depolarization and rise in cytosolic Ca^{2+} [132]. Since NMDA receptors are preferentially located on the distal processes of OL, the myelin sheaths are the most vulnerable targets for excitotoxic insults, leading to osmotic swelling, loosening, and vacuolation [205]. Activation of AMPA/kainate receptors, preferentially located in OL cell body, lead to an increase in intracellular Ca^{2+}, its accumulation within mitochondria, and consequent depolarization of this organelle with increased ROS production [207, 208]. Elevated levels of free radicals and Ca^{2+} overload in mitochondria lead to the opening of the permeability transition pore [209], an inner mitochondrial membrane channel that regulates exit of cytochrome *c* to the cytoplasm and other proapoptotic substances [210, 211]. This process leads consequently to activation of caspase-9 and -3 culminating in the execution of the intrinsic apoptotic cascade [211]. In addition, necrosis may be seen upon AMPA receptor activation [207, 211]. Sustained activation of P_{2x7} in the presence of excessive ATP induces an increase in intracellular Ca^{2+} that results in caspase-3 activation, chromatin condensation and cell death by apoptosis and necrosis depending on the intensity of the insult [212].

Excessive cytosolic Ca^{2+} can activate other pathways, such as calpains, phospholipases, endonucleases and NOS with consequent NO production (Fig. **3**). The reaction of NO with superoxide leads to the production of peroxynitrite that may promote oxidative toxicity in OL [213]. Calpains, which are intracellular Ca^{2+}-activated cysteine proteases, can mediate necrosis and caspase-independent apoptosis. These proteases cleave cytoskeletal proteins and proapoptotic members of the Bcl-2 family, like Bax [214-216], thus facilitating the release of the apoptosis-inducing factor from mitochondria, presumably through proteolytic cleavage of a membrane anchor that retains this factor on the inner mitochondrial membrane [217]. Other studies suggest that calpain activation can lead to cell death by necrosis due to lysosomal rupture and cathepsin-mediated cell death [218, 219]. Moreover, calpains can cleave numerous substrates including key components of the Ca^{2+} signalling system, like the plasma membrane Ca^{2+}-ATPase, leading to a decrease in Ca^{2+} removal from the OL cytoplasm [220].

4.1.2. Oxidative Damage

Several features are responsible for the high vulnerability of OL to oxidative damage. As described before, mitochondria depolariza-

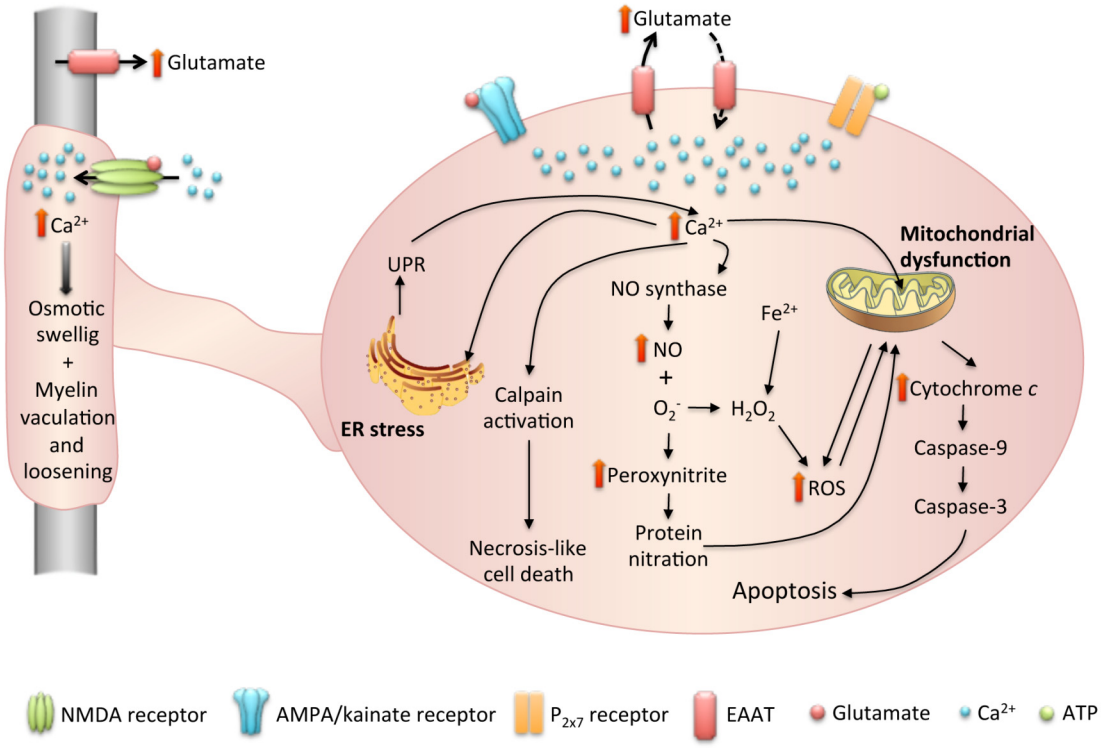

Fig. (3). Molecular mechanisms of toxicity to oligodendrocytes. Primarily, glutamate- and adenosine triphosphate (ATP)-induced toxicity to oligodendrocytes (OL) depends on excessive calcium (Ca^{2+}) influx, following activation of Ca^{2+}-permeable α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), kainate, *N*-methyl-*D*-aspartate (NMDA) and ATP activated P_{2x7} receptors. Increased concentrations of intracellular Ca^{2+} lead to mitochondrial dysfunction and consequent reactive oxygen species (ROS) production and caspase activation. On the other hand, iron (Fe^{2+}) can react with hydrogen peroxide (H_2O_2) with consequent production of hydroxyl radicals and oxidative stress. In addition, superoxide anion (O_2^-) reacts with nitric oxide (NO) leading to peroxynitrite formation that is toxic to OL. In addition, increased intracellular concentrations of Ca^{2+} can lead to calpain activation that mediates necrosis-like cell death or caspase-independent apoptosis. In situations of endoplasmic reticulum (ER) stress, the unfolded protein response program can fail leading to increased Ca^{2+} release from this organelle and augmented Ca^{2+} intracellular concentration. In situations of ATP depletion excitatory amino acid transporters (EAAT) revert their action leading to changes in ion gradients and consequent glutamate release from OL. The preferential location of NMDA receptors on the distal processes of OL turns the myelin sheaths particularly vulnerable to insults triggering osmotic swelling, myelin vacuolation and disruption.

tion by increased intracellular concentrations of Ca^{2+} leads to ROS production with deleterious effects in OL viability [207, 208]. OL consume large amounts of oxygen and ATP in order to produce myelin, which leads to the formation of hydrogen peroxide and other reactive oxygen species with toxic properties to these cells [221, 222]. On the other hand, OL have the largest intercellular stores of iron in the brain [221, 223], since it is used as co-factor for myelin synthetic enzymes [224]. Besides the critical role of iron in the myelin production, when in the presence of hydrogen peroxide it may trigger the formation of hydroxyl radicals by the Fenton's reaction. These radicals are very potent inducers of lipid peroxidation and, along with peroxidation products (e.g. 4-hydroxy-2-nonetal), are capable of impairing protein and acid nucleic functions, as well as promoting membrane destruction [225]. This effect is further amplified in OL by their low content of antioxidant defences, namely reduced glutathione [221, 226], an electron donor for the function of glutathione peroxidase that scavenges peroxides. OL have less than half of the glutathione content of astrocytes and <15% of the glutathione peroxidase activity [226]. Additionally, oxygen and NO radicals are particularly toxic to mitochondria through interaction and blockade of various proteins of the respiratory chain [227].

4.1.3. Endoplasmic Reticulum Stress

The ER is mainly recognized as a protein-folding factory, responsible for biosynthesis, folding, assembly and modification of several proteins [228]. However, during ER stress caused by accumulation of unfolded proteins or Ca^{2+} depletion, ER initiates the unfolded protein response (UPR) [229], in order to ensure the fidelity of protein folding and prevent accumulation of these non-functional proteins. In mammalian cells, three ER-localized protein sensors initiate UPR signalling: inositol-requiring enzyme 1α (IRE-1α), pancreatic ER kinase (PERK) and activating transcription factor (ATF)-6 [230, 231]. During ER stress, glucose-regulated protein (GRP)78, the best characterized ER chaperone protein, is sequestered through binding to unfolded or misfolded proteins, leading to the release and consequent activation of the ER stress sensors [232]. GRP78 dissociation leads to mobilization of ATF-6 for the Golgi and activation of IRE-1α and PERK through autophosphorylation. Activated IRE-1α induces X-box binding protein 1 (XBP1) splicing that translocates to the nucleus and binds to UPR elements in order to induce several UPR genes that assist in protein synthesis and secretion [233]. In situations of ER stress, ATF-6 is translocated to the Golgi complex where it suffers cleavage and its cytoplasmic fragment is released and translocated to the nucleus in order to activate the transcription of target genes [234, 235]. Finally, activated PERK initiates the phosphorylation, and consequent inactivation, of eukaryotic translation-initiation factor 2α (eIF2α), which in turns increases the expression levels of the transcription factor ATF-4 [236]. ATF-4 translocation to the nucleus upregulates the transcription of UPR target genes.

Curiously myelinating cells respond to ER stress in a distinct manner from other cell types. Activation of CCAAT-enhancer-

binding protein homologous protein (CHOP), a downstream effector molecule of the PERK signalling pathway, ~~in OL~~ promotes OL survival during ER stress [237], in contrast to the UPR-induced apoptotic demise triggered in other cell types. Moreover, OL activation of caspase-12, an ER-localized caspase, fails to contribute to OL apoptosis or myelin abnormalities in PLP mutant mice [238].

Accumulation of misfolded proteins in the ER can trigger Ca^{2+} release from this organelle, possibly through inositol-triphosphate receptors [239]. The Ca^{2+} released from the ER is accumulated in mitochondria and causes its depolarization, disrupting electron transport chain and increasing ROS production [240]. On the other hand ROS can in turn increase Ca^{2+} release from the ER by sensitizing ER Ca^{2+}-release channels and causing protein misfolding. This cycle of Ca^{2+} release, ROS production and protein misfolding act together to activate calpains [241], which in turn induce cell death as described before.

4.1.4. Cytokines

Although cytokines have some important roles in OL development, elevated levels of TNF-α and IFN-γ are correlated with OL toxicity and white matter defects.

As far as we know, the mechanism by which TNF-α causes toxic effects to OL lineage remains unresolved. While some studies found signals of TNF-α toxicity on cultured OL with a developmental-depend toxicity, others did not [242-245]. However, some authors demonstrated that increased concentrations of TNF-α have the ability to induce OL apoptosis both through the engagement of death receptors and by activation of sphingomyelinase and release of ceramide [245-247]. Another study has shown that recombinant TNF-α injection into the optic nerve leads to demyelination [248]. Recently, TNF-α was identified as a critical factor released by activated M1-polarized myeloid cells that decreases OPC survival, thus influencing OL differentiation [249]. In what concerns IFN-γ, the susceptibility of OL to this cytokine is more complex, since it is highly toxic for actively proliferating OPC, much less toxic for immature OL, and not toxic for mature OL [250].

Some evidences pointed out that cytokine-induced OL damage may be mediated by iron and involves mitochondrial dysfunction [251]. Indeed, the release of cytokines and free radicals diminish the glutamate uptake due to reduced expression of the glutamate transporters EAAT-2 (GLAST) and EAAT-2 (GLT1), thus resulting in elevated concentrations of this neurotransmitter and consequent overactivation of Ca^{2+}-permeable glutamate receptors that in turn leads to excitotoxicity [252].

4.2. Mechanisms Mediated by other Central Nervous System Cells

Toxicity to OL may also be mediated by other cell types in the environment being reactive astrocytes and microglia the most studied ones.

The role of reactive astrocytes and microglia in oligodendrogenesis remains unclear, but it is known that they are involved in OL toxicity through the release of highly reactive oxygen/nitrogen species and pro-inflammatory cytokines like TNF-α [253-255]. Activated microglia show altered glutamate metabolism producing the enzyme glutaminase and the glutamate-cystine exchanger xCT^-, which result in impaired expression or function of glutamate transporters, together with a consequent disruption of glutamate homeostasis and excitotoxicity [252, 256, 257]. In addition, microglia also express ATP P_{2x7} receptors that besides having an important role in microglial proliferation and activation [258] are also linked to the release of several substances including pro-inflammatory cytokines. Finally, activated microglia may reduce OL survival through the release of peroxynitrite that is toxic to OL [213].

Despite the fact that astrocytes are generally considered protective by releasing trophic factors such as LIF, some studies are now pointing out a pathological role for reactive astrocytes in white matter diseases. A recent work demonstrated that exogenous levels of TNF-α do not cause significant pre-OL death in contrast with cultures where these cells are in contact with astrocytes. These data suggest a role for astrocytes in promoting toxicity to OL via TNF receptor 1 activation in a contact-dependent manner [259]. This contact-dependent toxicity can be due to the presence of gap junctions since they are known to couple astrocytes and OL [260, 261] and to be involved in the propagation of cell injury [262, 263]. Moreover, when regeneration is not possible or the damage is too big, astrocytes may limit remyelination and CNS repair, through the formation of a glial scar, a physical barrier against inflammatory cells entering in demyelinated areas, which prevents OPC migration and maturation as well as axonal regeneration [264, 265].

5. OLIGODENDROCYTE INVOLVEMENT IN SOME NEUROLOGICAL DISORDERS

Since OL and their ability to myelinate neuronal axons are so important for the fast conduction of the action potential and the maintenance of the axonal integrity, their pathophysiology is emerging as a key event in the occurrence of neurological disorders. Defects in myelin insulation can lead to several CNS disorders along life journey. Indeed, impairment of OPC and OL function may occur during the perinatal life, in conditions such as periventricular leukomalacia (PVL), hypoxia/ischemia (HI) and neonatal hyperbilirubinemia that can trigger the emergence of long-lasting neurological and neurodegenerative conditions, such as schizophrenia, multiple sclerosis (MS) and Alzheimer disease (AD).

5.1. Periventricular Leukomalacia

PVL is traditionally classified as a white matter disorder and is the most common manifestation of brain injury that occurs in preterm infants, typically those born at a gestational age of 24-32 weeks with a body weight at birth of less than 1,500 g [43, 266]. PVL influences the development and maturation of myelin in thalamus, basal ganglia, cerebral cortex and cerebellum that may result in neurological deficits due to neuronal loss and axonal damage [267]. PVL consists of two basic components, focal necrosis deep in periventricular white matter with loss of all cellular elements, and a more diffuse and cell-specific lesion, consisting of an acute loss of pre-OL, which comprises about 90% of all OL during the high-risk period for PVL [43, 268], with accompanying astrogliosis and microgliosis [269-272]. The diffuse focal necrosis can be microscopic in size (several millimetres or more) and evolve over several weeks to multiple cystic lesions, being known as cystic PVL. Current data indicate that the incidence of cystic PVL is declining and is observed in less than 5% of infants with very low birth weight [273-276]. In contrast, non-diffuse focal necrosis is emerging as the predominant lesion. This condition, termed non-cystic PVL, is characterised by marked astrogliosis and microgliosis and evolve over several weeks to glial scars that are not readily seen by neuroimaging. In both PVL conditions, injury to pre-OL occurs since these cells are even more susceptible than mature OL. This vulnerability is related with: (1) the existence of amplified oxidative damage as result of a developmental deficit in superoxide dismutases and of hydrogen peroxide-scavenging deficit [277-279] combined with active iron acquisition [224]; (2) higher vulnerability to reactive NO species attack by direct mitochondrial toxicity with translocation of apoptosis inducing factor [280] and formation of peroxynitrite [213, 281]; (3) significant developmental upregulation of non-NMDA glutamate receptors [138, 282] accompanied by enhanced AMPA-mediated Ca^{2+} signalling, which increases excitotoxicity [283] and (4) transient increase in EAAT2, which may become another source of glutamate under pathological conditions [284]. Pre-OL injury results in cell death or process loss (with intact soma) [281, 285-288]. However, pre-OL may survive with loss of cell processes but these cells do not appear to differentiate subsequently [288]. In addition, some OL may synthesize MBP, but are not able to do a proper myelination due to impairment in MBP lo-

calization [288]. The cell loss is mainly related with AMPA receptors activation in cell soma [137, 289-291], while processes loss is associated to NMDA receptors activation on pre-OL ramifications [139, 292, 293]. The ultimate result of these disturbances in pre-OL development is a deficit in mature OL with consequent cerebral hypomyelination, the hallmark of PVL. Another source of damage to pre-OL in PVL is microglia activation, especially as the number of microglia in cerebral white matter peaks during the period of highest vulnerability to PVL [294]. Reactive astrocytes, microglia and macrophages also damage pre-OL by the release of IFN-γ that leads to an increase in inducible NOS [295].

The aetiology of PVL is multifactorial but HI is considered one of the primary causes that can lead to microglial activation, cytokine release, excitotoxicity and free radicals attack to OL, the major causes of OL damage as indicated above.

5.2. Hypoxia/Ischemia

HI is an important cause of perinatal brain injury both in term infants suffering from intrapartum asphyxia and in preterm infants exposed to hypotensive events [271]. Moreover, premature infants are especially vulnerable to brain injury due to HI, particularly in white matter. This propensity relates to underdeveloped lungs that often cannot deliver enough oxygen and a heart that is relatively weak in pumping blood to the brain, as well as insufficiencies in processing oxygen and in energy metabolism. Additionally, white matter is particularly affected since distal fields in this region are not fully developed, which leads to very low basal values for blood flow to cerebral white matter in premature infant.

The pathophysiological mechanisms of HI are complex and processes such as apoptosis, necroptosis (a form of regulated necrosis), mitochondrial impairment, oxidative stress and inflammation are involved [296].

Pre-OL are acutely damaged by short periods of HI. After 30 min of arterial occlusion is possible to observe swelling, and a large number of OL die within a few hours [297]. Indeed, 90% of OL die within 3 h of oxygen-glucose deprivation [298]. Furthermore, the increasing developmental resistance of cerebral white matter to HI is related to the onset of pre-OL differentiation to myelinating OL that display reduced susceptibility to HI [268]. Although it was initially hypothesized that persistent loss of pre-OL was the origin of abnormal myelination, subsequent findings have supported an alternative mechanism where myelination disturbances involve a potentially reversible process linked to arrested pre-OL maturation. Despite substantial acute and delayed pre-OL degeneration after HI, surviving pre-OL in preterm-equivalent rats rapidly increased in number to regenerate depleted pre-OL [299, 300]. This expansion appeared to be driven mostly by pre-OL that proliferated locally at the sites of white matter [299] and cortical injury [301] rather than from the subventricular zone, where less robust generation of OL has been observed [302, 303]. Regeneration of pre-OL from the surviving cells compensates its death, but these newly generated pre-OL display persistent arrested differentiation and fail to myelinate intact axons.

The excitotoxicity mediated by glutamate receptors is the principal mechanism for pre-OL death exposed to oxygen-glucose deprivation *in vitro* [137, 304, 305], while blockade of NMDA and AMPA/kainate receptors prevents OL death and myelin loss during ischemic injury [282, 298, 306, 307]. Glutamate-mediated axonal injury appears to be related with a mechanism of excessive glutamate release from OL and axons [292, 308], indicated as the major sources of extracellular glutamate during HI energy failure. Moreover, ischemia leads to an energy crisis and consequent lactic acidosis that result in mobilization of protein-bound iron stores. This increases the levels of cytosolic iron that participates in Fenton's reaction [309, 310] leading to oxidative stres.

As described before, OL are extremely sensitive to disruptions in intracellular Ca^{2+} homeostasis. In HI, metabolic stress and energy crisis lead to prolonged overstimulation of neurotransmitter receptors, resulting in an increase in cytosolic Ca^{2+} that is worsened by the activation of voltage-gated Ca^{2+}channels and the reversal of the Na^{+}/Ca^{2+} exchanger [311]. This Ca^{2+} is sequestered by mitochondria and leads to mitochondrial bioenergetic dysfunction, which is characterized by impaired oxidative phosphorylation, ROS generation, release of apoptogenic proteins and consequent cell death by apoptosis or necrosis [312, 313]. Although, it is clear that caspase-mediated mechanisms of apoptosis contribute at least in part to acute pre-OL death from HI, the magnitude of caspase activation differs among studies and appears to be related to the severity of the insult [268, 299, 314-316].

During ischemia, ATP-mediated toxicity to OL can also occur, mainly via P_{2X7} receptor. Sustained activation induces cell death, myelin damage and white matter injury [212, 317, 318]. Furthermore, ATP release by OL during ischemia leads to depolarization of mitochondria and generation of ROS [317]. ATP released by dying cells can continue to aggravate P_{2X7}-mediated injury [319]. In HI, oxidative stress is characterized by enhanced production of the superoxide radical, lipid peroxidation, and reduction of Fe^{3+} to the oxidant Fe^{2+} [320]. Pre-OL are the most susceptible cells from OL lineage to HI. A recent study has shown that oxygen-glucose deprivation lead to disarrangement of MBP distribution, decreased levels of phosphorylated MBP and disturbed capacity to contact with neurons [321]. Additionally, mice exposed to chronic hypoxia show OL regeneration and the return of myelin proteins to normal levels within a few weeks after the injury, but myelin structure is abnormal [322]. Interestingly, mice genetically altered to mimic high local oxygen tension in OL lineage cells display arrested OPC maturation and subsequent hypomyelination, developing white matter disease resembling cystic PVL [323].

5.3. Neonatal Hyperbilirubinemia

Hyperbilirubinemia or jaundice is a frequent condition during the neonatal period that affects 60% of full-term newborns and 80% of preterm infants [324, 325], although neurological injury is rarely seen in healthy infants with serum bilirubin levels below 25 mg/dL [5]. The current understanding on the development of bilirubin encephalopathy is that when the level of serum unconjugated bilirubin (UCB) exceeds the bilirubin binding capacity of albumin, occurs an increase in the amount of unconjugated unbound UCB (free bilirubin), therefore increasing its passage across the blood-brain barrier (BBB) and saturating the brain cellular defensive mechanism. In these conditions, either UCB uniformly distributes in the brain parenchyma bilirubin-induced neurological dysfunction (BIND) or specifically precipitates in some areas such as basal ganglia, central and peripheral auditory pathways, hippocampus, diencephalon, subthalamic nuclei and cerebellum (*kernicterus* or bilirubin encephalopathy), thus resulting in lesions that may be reversible or not, depending on opportune intervention therapies, duration, developmental age, and concomitant pathologies [4, 326, 327]. BIND and *kernicterus* can thus culminate in neonatal death or multisystem disabilities, including athetoid cerebral palsy, as wel as speech, oculomotor, auditory, and other sensori-processing disabilities [5]. Interestingly, concerns about subtle manifestations of BIND, due to levels of hyperbilirubinemia that are not generally considered severe enough to indicate treatment, or to prolonged exposure to lower levels of bilirubin in a vulnerable infant, have already been validated in previous studies [328-330]. A recent work has demonstrated that bilirubin levels falling short of developing acute bilirubin encephalopathy affects neurodevelopmental outcome, with a proportional increase in the abnormal developmental quotient and peak of serum bilirubin [331]. These results corroborate previous studies, which demonstrated that neonatal jaundice could have an impact in learning and memory and changes in long-term cognitive ability [332, 333]. Long term consequences of hy-

perbilirubinemia above 20 mg/dL in newborns ≥2500 g birth weight and ≥37 weeks of gestation include neurobehavioral disorders (hyperactivity/impulsivity and inattention at childhood) and cognitive abnormalities (problems with reading, writing and mathematics) in adulthood [334]. In fact, an increased risk of psychological development disorders, especially autistic disorders, was observed for children exposed to jaundice during neonatal life [335-337]. Moreover, schizophrenia has also a higher incidence in patients that developed neonatal jaundice when compared with patients without jaundice [338].

UCB accumulation in the brain triggers cell death in neurons, astrocytes, microglia and OL [339-343]. Regarding to mechanisms of UCB toxicity some studies have demonstrated that UCB leads to oxidative stress, release of glutamate and long-lasting alterations in neuritic arborisation [327]. Both astrocytes and microglia respond to UCB exposure by releasing pro-inflammatory cytokines [339, 340]. The cascade of events implicated in glial reactivity involves TNF-α and IL-1β receptor signalling pathways [344], as well as activation of mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)-κB [345, 346].

Concerning the UCB effects on OL, we have demonstrated that UCB induces an increase in OPC death by apoptosis and necrosis-like cell death, involving early signals of ER stress and mitochondrial dysfunction and later activation of calpains, without inflammatory response or glutamate release [341] (Fig. **4A**). Moreover, UCB impairs OPC differentiation into myelinating OL, as well as the morphological maturation process of OL by impairment of process extension, reduction of the myelin membrane surface and diameter of mature OL [347] (Fig. **4B**). Consequently, UCB causes myelination deficits evidenced by a decrease in both the number of myelinated internodes per OL and the internode length in an *in vitro* myelination model composed of a co-culture of dorsal-root ganglion neurons and OL [347] (Fig. **4C**). One of our recent studies performed in *ex vivo* cerebellar slice cultures have also demonstrated that UCB is able to trigger an increase in immature OL, a decrease in the number of myelinated fibres and an increase in astrogliosis and microgliosis [348] (Fig. **4D**). Most attractive, UCB-induced myelination impairment involved the activation of TNF-α and AMPA signalling pathways [348]. In addition, there are some evidences that UCB can lead to changes in human white matter. Recent results have demonstrated that myelination is altered in a premature infant with *kernicterus*, showing a decrease in the density of myelinated fibres and loss of axons in the cerebellum [349]. These findings are in line with previous studies demonstrating that cerebellum is the most common pigmented region of the brain in *kernicterus*, after basal ganglia, with a marked decrease in the number of neurons, an increase in gliosis and a reduction in the myelination pattern [350]. Moreover, white matter volume reduction and delay in hemispheric myelination was also observed in infants with severe UCB encephalopathy outcomes [351]. To this regard, it was demonstrated that UCB is able to bind mainly to MBP and that high concentration of this pigment is found in the myelin fraction of rat brains injected with UCB [352, 353]. In more detail, an early study performed in an experimental model of *kernicterus* showed that this condition lead to significant changes in myelin sheath, with separation of myelin lamellae, suggesting that its compaction did not properly occurred [354]. Interestingly, another study in Gunn rats, an animal model of *kernicterus,* using electronic microscopy showed that myelin figures were present as tongues or remnants of cytoplasm and irregular spaces or vacuoles. This study also revealed the presence of myelin around vacuoles, bits of cytoplasm and other cytoplasmic debris [355].

5.4. From neonatal Damage to Neurological and Neurodegenerative Diseases

Although there are marked changes in myelination during the perinatal period that can be easily identified by the clinicians and give the diagnosis of a sequelae during young childhood, if the myelin alterations are very subtle they may pass unnoticed and give rise to later neurologic conditions or even be a first trigger for future neurodegenerative disorders.

5.4.1. Schizophrenia

Schizophrenia is considered a severe psychiatric disorder due to its chronic course and often poor long-term outcomes in social and vocational realms [356]. Furthermore, schizophrenia is the most common psychotic illness, with approximately 7 in 1000 people developing the disorder in their lifetime [357]. This condition is characterized by: 1) positive symptoms, such as delusions, hallucinations and disorganized speech/thinking; 2) negative symptoms, like social withdrawal, anhedonia and blunted affect; and 3) cognitive dysfunction, including deficits in attention, working memory and executive function [358].

The exact cause for schizophrenia is still unknown. However, their association with previous exposure to prenatal infection was demonstrated [359] and a toxic role of cytokines in neurite formation [360], which is in accordance with the neuropathology of this disease. In addition, the incidence of schizophrenia is increased in patients that present Gilbert syndrome, a UDP-glucuronosyl transferase activity deficiency that leads to mild hyperbilirubinemia [361], or had hyperbilirubinemia during the neonatal period [338, 362]. More recently, it is hypothesized that the aetiology of schizophrenia is the result of both abnormalities in local neuronal activity within various brain regions and dysfunctional interactions between cortical and subcortical circuits [363], probably due to alterations in brain development during foetal/neonatal life long before manifestation of illness in adolescence or early adulthood is observed [364].

Concerning to changes in neuronal circuits, impairment in synapse formation and plasticity has been implicated in schizophrenia [365-368]. In addition, it is accepted that dopaminergic activity can modulate symptoms of schizophrenia, although the degree to which dopaminergic activity is a primary or secondary consequence of the disease is still unsolved. However, some studies identified neuroanatomical changes in prefrontal cortex due to loss of glutamatergic pyramidal cell spines and axons, loss of GAGAergic interneurons and decreased mesocortical dopaminergic innervation, while others attributed cognitive impairments to cell loss within thalamic subregions and subsequent decrease in excitatory thalamic afferents to the prefrontal cortex [369-371]. Alterations in glutamatergic, GABAergic and dopaminergic signalling have also been reported, leading to loss of neuronal connections and neurons in other brain regions, like hippocampus, striatum, amygdala as well as in auditory and visual cortex [372-376]. This disorder leads to an increase in dopamine release in the striatum in parallel to its depletion in prefrontal cortex [377]. Another important feature observed is a decreased NMDA receptor function in subcortical regions, disinhibiting glutamate and dopaminergic signalling in the cortex, with consequent sensory, cognitive and behavioural deficits [378-380].

Although most studies in schizophrenia brain defects were focused on alterations in neurons and grey matter, more recent reports also implicate defects in white matter damage, including the fibre bundles of the internal capsule and corpus callosum, which are strongly associated with abnormal or decreased structural and functional connectivity [6, 381]. Indeed, given the clear impact that changes in glutamate have on neuronal plasticity and synaptic connectivity, it can be postulated that it may compromise the integrity of the white matter by directly acting on OL. Moreover, disorganized thought and cognitive impairments observed in schizophrenia can be related with altered conduction velocity [382], since defined conduction velocity is necessary for several learning processes [383]. Indeed, specific abnormalities in myelin are increasingly observed in patients with schizophrenia [384], including decreased numbers of OL [385]. Additionally, the expression levels of Olig2, MBP, MOG and MAG are lower in dorsolateral prefrontal and

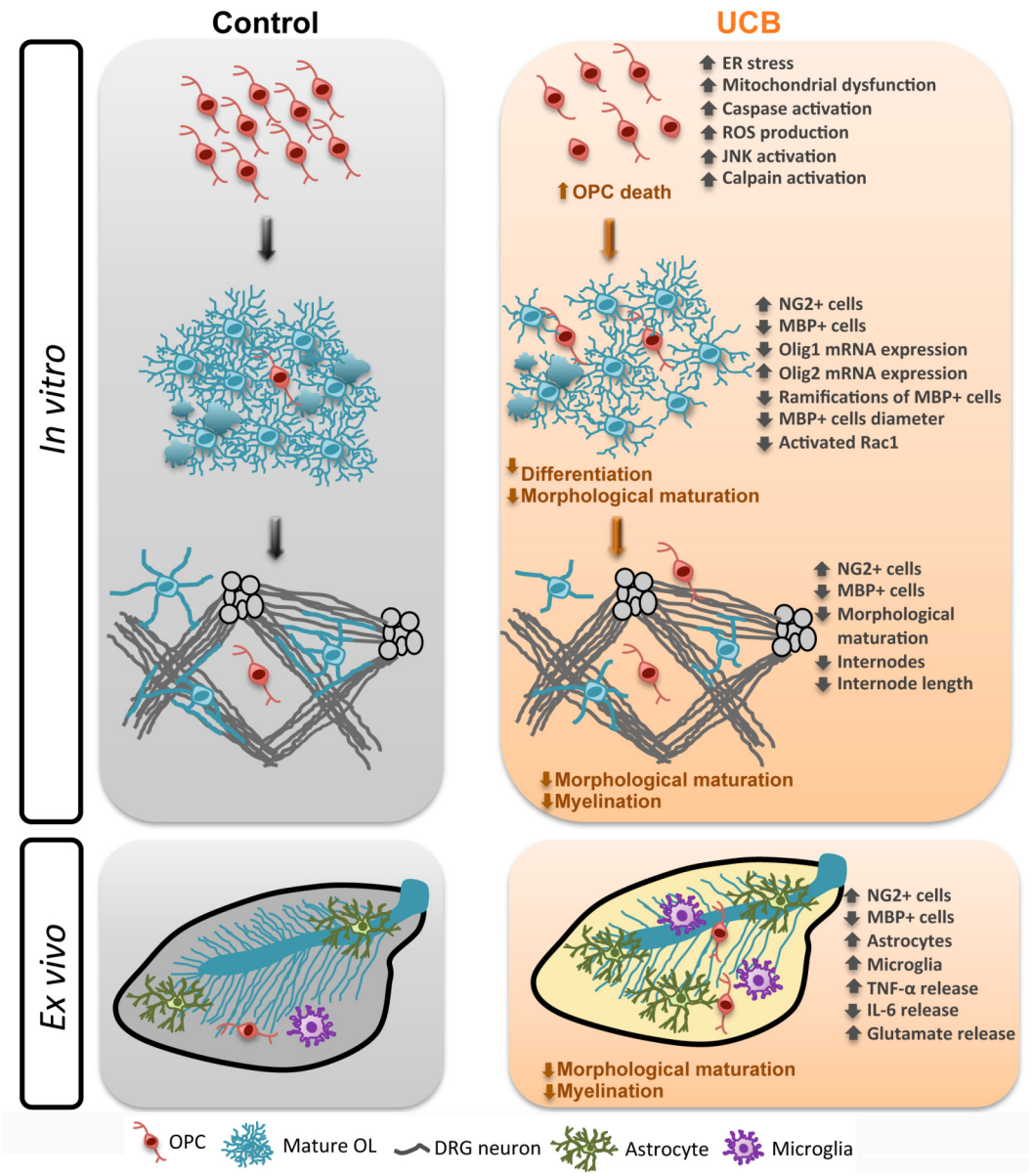

Fig. (4). Schematic representation of the major effects produced by unconjugated bilirubin (UCB) in oligodendrocyte (OL) development. *In vitro* studies using oligodendrocyte precursor cell (OPC) primary cultures, in oligodendrocyte (OL) maturation model and in dorsal root ganglia (DRG) neuron-OL co-culture, showed that UCB causes OPC death, decreased differentiation and reduced myelination, respectively. In addition, *ex vivo* studies developed in cerebellar slice cultures demonstrated that UCB exposure induces a decrease in OL morphological maturation and myelination, probably as a result of astrocyte and microglia activation.

cortex and visual cortex of patients with schizophrenia when compared with control subjects [386-388]. Moreover, is has been shown in the last years that even the molecular and functional organization of the nodal, paranodal and juxtaparanodal regions are affected in schizophrenia patients. In this context, the expression of contactin 2 and Nav1.6, which participate in the formation and maintenance of nodes of Ranvier and adherens junctions, as described before, are diminished in the brains of schizophrenia patients [389]. Decreased AnkG expression was also found in the cortical layers of persons with schizophrenia [390]. Many studies have demonstrated impairment in white matter integrity and in organization at several brain regions, including prefrontal, temporal and occipital lobes [391-394], as well as reduced white matter tracts connecting corticothalamic and cortolimbic structures, evidencing the disconnection of these networks [395]. A recent study performed in an animal model of schizophrenia demonstrated myelination impairment with a decrease in MBP expression [396]. The possible explanation for the decreased white matter and the down expression of myelin-related genes in this disorder is that OL are either present in reduced number or are dysfunctional. Interestingly, some authors have already shown that patients with schizophrenia present a more disperse arrangement of OL and lower density of OL in grey matter, in white matter at the superior frontal gyrus [397], in anterior cingulate cortex [398] and in anterior thalamic nucleus [399]. By electron microscopy it was possible to observe damaged myelin sheath lamellae forming lamellar bodies in schizophrenic brains, as well as irregularities in OL mitochondria and their apoptosis [400]. Finally, ultrastructural studies showed OL loss in the fascicular white matter, with shrinkage in the diameter of neuronal axons [401], confirming myelination alterations in schizophrenic patients.

Any of these alterations ultimately result in changes in nerve conductivity, leading to abnormalities of nerve transmission along the myelinated fibres in the circuitries, as well as aberrant connectivity and disorganized axonal trajectories, which are consistent with findings of white matter abnormalities in schizophrenia brains by imaging studies [402]. Moreover, compensation and adaptation to these abnormal processes may occur at the cell and circuitry levels that altogether contribute to schizophrenia phenotypes [403].

Although it is clear that there is not a single locus of dysfunction within the schizophrenic brain, several questions remain to be elucidated, principally the identification of factors leading to OL and neuronal dysfunction, the most affected cells.

5.4.2. Multiple Sclerosis

MS that is the most common neurological disease between young adults (with ages between 20 and 40 years) has a worldwide prevalence estimated between 1.3/1000 cases in the developed world [404]. MS is a very complex disease, with variable onset and clinical course that involve several pathophysiological mechanisms, including axonal/neuronal damage, demyelination, inflammation, gliosis, oxidative stress and excitotoxicity, followed by remyelination and repair, together with immune system alterations and BBB disruption [405, 406]. The first symptoms of the disease are episodes or relapses of symptoms like impaired vision and deficits in sensation, but disease progression can lead to severe disabilities as paralysis, memory loss and incontinence [407]. Besides the course of this disease is highly variable, most patients initially present a period of relapsing-remitting MS (RRMS). However, after 10-15 years, the disease becomes progressive (secondary progressive MS, SPMS) in up to 50% of untreated patients. However, about 10 to 20% of MS patients have progressive disease ~~progression~~ since the disease onset with no relapse or remission episodes (progressive MS, PPMS) [408]. RRMS is dominated by multifocal inflammation and cytokine physiological actions [405] through the gradual accumulation of these biomolecules at this phase and consequent irreversible neurological deficits, leading to SPMS that is characterized by clinical attacks and remissions, with progression of the clinical symptoms [409, 410]. PPMS is generally characterized by a lesser degree of inflammation and a greater proportion of axonal loss, even during the early disease course [411].

Although the aetiology of MS remains elusive, plaques of inflammatory demyelination within the CNS are considered the pathologic hallmark of MS, being destructed myelin an essential element within these plaques [412]. Some studies also reveal that BBB is a key structure [413], since the entry of cells from the immune system into the CNS is a critical step for the onset of the disease especially during the acute phases. Relapses are fundamentally a manifestation of an inflammatory response occurring mostly in the white matter, but also in the myelin tracts of the grey matter resulting in focal demyelination and relative axonal sparing. During the past years, MS research has mostly focused on the role of CD4+ T cells in the disease pathogenesis. Immune phase begins with CD4+ T cells activation in response to dendritic cells that take up the exogenous or endogenous antigen in order to present it to the immune cells. As a result, CD4+ T cells become activated and secrete IFN-γ, TNF-α, TGF-β, IL-10 and IL-17 [414]. Moreover, T cells from MS patients can recognize MBP [415, 416], PLP [417] and MOG [418]. These cells have also the ability to stimulate microglia, macrophages and astrocytes and to recruit B cells, ultimately resulting in demyelination and damage of OL and axons with concomitant neurological deficits [419]. Moreover, B cells may directly participate in the demyelination process by secreting pathogenic antibodies that target OL with or without the presence of complement [420]. A recent study have also demonstrated that FGF-9 can induce the production of pro-inflammatory chemokines, which in turn contribute to microglia and macrophage recruitment into MS lesions and consequent appearance of pre-myelinating OL that are able to interact with axons but fail the myelin sheath assembly [421].

Demyelination has long been considered a marked feature of MS in proportion to the loss of axons. However, axonal damage is an important finding in this disease that correlates with its progression and permanent neurologic disability in patients [422]. In fact, some studies proposed that axonal impairment occurs in areas of active inflammatory demyelination and in an early phase of the disease course [423]. This axonal loss contribute to the clinical decline observed in MS patients, since a reduced number of surviving corticospinal axons are correlated with high levels of motor disability [424]. The exact mechanism by which axonal damage arises is not completely solved. Nevertheless, some studies have already shown that Na^+ channel clusters are no longer stable at nodes in MS, what is thought to contribute for axonal degeneration [425, 426]. Another study performed in an animal model of MS showed a decrease in the developmental switch from Nav1.2 to Nav1.6 [427]. Since antibodies against Nfasc have been described in MS, another possible explanation for node disruption is that these antibodies are disrupting the localization of Na^+ channels and consequently the nerve conduction [428]. MS patients present also disruption of panodal organization due to loss of Caspr [426, 429], decreased levels of NfascNF155 with decreased lipid raft association [430, 431] and disrupted K^+ channel localization [426]. In other hand, axonal damage can be induced by CD8+ T cells via the release of cytotoxic granules, induction of apoptosis through activation of surface receptors, the release of cytokines from surrounding glia or immune cells, or direct transection of axons [432, 433]. Moreover, microglia can also release toxic molecules such as glutamate, proteases, TNF-α and nitrogen species leading not only to axonal degeneration but also to OL injury, demyelination and BBB dysfunction [434]. In fact, glutamate is increased in plaques and normal appearing white matter of MS patients [435, 436]. As a consequence of the immune injury to myelin, glutamate mediated toxicity and higher energy demands may further increase the damage [437].

Although little is known about the association of perinatal conditions with ~~multiple sclerosis~~, a few reports suggest that exposure of the immature brain to inflammation, namely microglia activity, may enhance the CNS vulnerability for the development of a neurological disorders including MS [438].

5.4.3. Alzheimer Disease

AD is the most frequent cause of senile dementia in elderly people over 65 years old, representing 60 to 80 % of the cases. In 2010, approximately 5.5 million of people live with dementia worldwide [439]. Taking into account that both established and developing nations are rapidly aging, the frequency is expected to almost double every 20 years, reaching values of 65.7 million in 2030 and 115.4 million in 2050 [439]. In people over 65 years old the prevalence of AD is around 4.4% [440], doubling for every 5 years [441]. AD is a progressive neurodegenerative disorder that usually begins with difficulty in the ability to remember newly learned information because this disease changes typically begin in the part of the brain that affects learning. However, as AD advances through the brain it inevitably affects all intellectual function and leads to complete dependence for all basic functions of daily life and premature death, as severe symptoms include disorientation, deepening confusion of time and place, serious memory loss, difficulty speaking, swallowing and walking [442, 443]. The main pathological manifestations of AD include extensive neuronal loss and synaptic dysfunction [444], oxidative stress [445], imbalance of metal ions [446], disturbances of cholesterol and lipid metabolism [447], damage of cellular membranes by amyloid toxins [448], neuroinflammation [449], extracellular β-amyloid (Aβ) that form senile plaques following the amyloidogenic cleavage of amyloid precursor protein (APP), and deposits of mictotubule-associated protein tau that forms neurofibrillary tangles (NFTs) [450].

Research on AD has mostly focused in Aβ accumulation and its induction of the neuronal damage, being widely believed that AD is initiated as a synaptic dysfunction that correlates with memory loss in the early stages of the disease and structural damage of the brain at the later stages of AD [451]. Nevertheless, as senile plaques contain also activated microglia at the centre and is surrounded by a crown of activated astrocytes, the importance of these glial cells gained recognition in the last few years [452, 453]. In this context, glial activation leads to sustained production of proinflammatory molecules and consequently to a chronic inflammatory process. In addition, it has also been shown the presence of dystrophic microglia in humam brain autopsy samples from AD patients that probably result in a reduced ability to clear altered proteins from the CNS [454].

Regarding to OL and myelin, some *in vivo* studies in AD models shown that myelin and OL lineage alterations occurs first than the appearance of Aβ and tau pathology [455, 456]. In fact, it has been suggested that myelin breakdown releases iron and consequently promotes the development of toxic Aβ fibrils that can deposit in the brain, enhancing the formation of senile plaques, which in turn destroys more myelin [457]. Besides immunohistochemical and *in situ* hybridisation studies have shown that APP is mainly expressed by neurons [458, 459], some studies have revealed the presence of APP-reactive OL in white matter and APP mRNA transcripts in OL, respectively [459, 460]. More recently, Skaper el al have demonstrated that rat cortical differentiated OL *in vitro*, express not only APP protein, but also secrete Aβ40 and Aβ42 to culture media in amounts similar to those found in cultured cortical neurons [461]. Furthermore, Aβ is able to activate the neutral sphingomyelinase-ceramide cascade via an oxidative mechanism and consequently induce OL dysfunction [462]. Exposure of OL to Aβ induces also cell death and morphological changes suggestive of damage like breakdown of OL processes and appearance of shrunken cell bodies [463]. Desai *et al* have also shown that Aβ leads to an increase in caspase-3 expression and apoptotic cell death of OPC [455]. As referred before, oxidative stress is a hallmark of AD and the molecular mechanism of OL cell death probably also involves oxidative stress, since OL are particular susceptible because their reduced glutathione content and high iron concentration and consequent impaired ability to scavenge oxygen radicals. In addition, Aβ has increased ability for damaging cholesterol rich membranes like the ones found in OL and myelin [464]. Several studies have already demonstrated the presence of white matter lesions and myelin abnormalities in the brain of AD patients [465-468]. It is also known that total amounts of protein, lipids and cholesterol were significantly reduced its composition in AD patients [469, 470]. A strong correlation between Aβ levels and myelin damage was found in postmortem brain tissue of patients with AD [466]. In fact, myelin disruption and intracellular lipids deposits in AD have been described early by Alzheimer *et al* [471] and after that another studies shown that AD patients present a great loss of myelin integrity [472], which precedes the onset of cognitive impairment [473]. Analysis of postmortem brain tissue of AD showed a decrease in MBP, PLP and CNPase levels [466, 474] and consequent regional atrophy of the corpus callosum [475]. More recently, Zhan *et al* have shown that AD patients present a significant reduction in intact MBP and consequently an increase in degraded MBP in periventricular white matter adjacent to a denuded ependymal layer together with the appearance of increased number of vesicles containing degraded MBP, myelin lipid and neurofilament [476]. In other hand, myelin can also be altered in AD due to changes in the communication between axons and OL. In this context, a recent study reported that in different animal models of AD the expression of Ank-G is downregulated, being this protein essential for the formation of the node of Ranvier and consequently a proper myelination [477].

Curiously, a few reports bridge changes during the neurodevelopmental age with the later emergence of AD. Martisova and colleagues showed that neonatal stressed animals showed changes in CNS growth factors and synaptic density which were associated with increased levels of Aβ or hyperphosphorylation of tau in the brain of those aged animals [478]. In addition, also a disproportionate activation of microglia during neurodevelopment of young adulthood may be beyond an altered CNS response later life determining the cognitive decline during AD [479].

CONCLUSION

OL have the important function of axon myelination that is critical not only for OL development and maintenance, but also to support axons and sustain their structural integrity and survival. OL have a highly regulated process of differentiation and maturation in order to be able to myelinate the axons. In order to myelinate properly, OL have a high metabolic rate turning these cells very susceptible to oxidative, excitotoxic and inflammatory damage. Taking all these aspects into account several targets for OL protection and induction of OL maturation and myelination can be developed in order to prevent or attenuate OL damage and myelin injury. However, further studies in animal models of specific diseases that involve impairment of OL development and myelination as well as well-designed clinical trials are essential to extrapolate the findings obtained on experimental models to human neurologic diseases.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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