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REVIEW PAPER

Ca^{2+} Signaling in Oligodendrocyte Development

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Abstract

Calcium signaling has essential roles in the development of the nervous system, from neural induction to the proliferation, migration, and differentiation of both neuronal and glia cells. The temporal and spatial dynamics of Ca^{2+} signals control the highly diverse yet specific transcriptional programs that establish the complex structures of the nervous system. Ca^{2+}-signaling pathways are shaped by interactions among metabotropic signaling cascades, ion channels, intracellular Ca^{2+} stores, and a multitude of downstream effector proteins that activate specific genetic programs. Progress in the last decade has led to significant advances in our understanding of the functional architecture of Ca^{2+} signaling networks involved in oligodendrocyte development. In this review, we summarize the molecular and functional organizations of Ca^{2+}-signaling networks during the differentiation of oligodendrocyte, especially its impact on myelin gene expression, proliferation, migration, and myelination. Importantly, the existence of multiple routes of Ca^{2+} influx opens the possibility that the activity of calcium channels can be manipulated pharmacologically to encourage oligodendrocyte maturation and remyelination after demyelinating episodes in the brain.

Keywords Calcium · Oligodendrocyte · Myelination · Voltage-operated Ca^{2+} channel · G-protein-coupled receptor

Introduction

Oligodendrocytes (OLs) are the myelinating cells in the central nervous system (CNS) and myelin structure is required to enable saltatory conduction of action potentials, as well as to provide long-term trophic support for axonal integrity maintenance (Nave and Werner 2014). Disruptions in myelination or failure of remyelination after injury contribute to a broad spectrum of debilitating neurological diseases, such as multiple sclerosis and leukodystrophies (Nave and Werner 2014; Franklin and Gallo 2014). During CNS development, OLs arise after a series of carefully choreographed steps of lineage progression from oligodendrocyte precursor cells (OPCs) to immature OLs and finally to mature myelinating OLs.

Calcium ions are universal second messengers regulating wide range of important eukaryotic cells functions, and the last decade has seen the identification of important roles for calcium signaling in nearly every aspect of oligodendrocyte development, such as proliferation, migration, and initiation of myelination (Agresti et al. 2005a, b; Cheli et al. 2015, 2016). As one of the responding mechanisms to neuronal activity (de Faria et al. 2019), calcium can translate neuronal activity into intracellular ion signaling in OPCs, and trigger the response in oligodendrocyte, which in turn modulates neuronal activity. There are several potential mechanisms of Ca^{2+} elevation in OPCs, including direct influx through plasma membrane voltage- or ligand-gated channels and release from internal Ca^{2+} stores (Fig. 1). This review assesses the literature on the major pathways of Ca^{2+} influx, which orchestrate the key effector functions of oligodendrocyte development.

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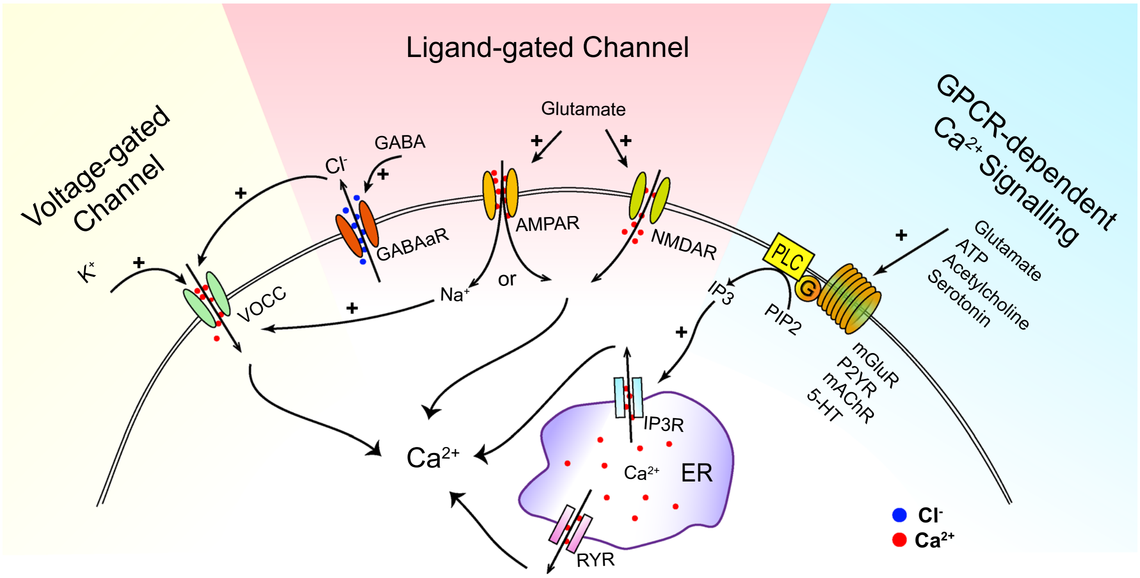

Fig. 1 Multiple pathways demonstrating response to neuronal activity-induced increase in intracellular calcium in oligodendrocytes. Neuronal depolarization results in activity-dependent calcium dynamics in oligodendrocyte. OPCs express not only ion channels, but also receptors of neurotransmitter, which make oligodendrocytes equipped to respond to neuronal activity. Cell membrane depolarization can activate voltage-gated channels (VOCCs) and then increase cytosolic calcium. Neurotransmitters, including GABA, glutamate, ATP, acetylcholine, and Serotonin, have been shown to increase intracellular calcium in OPCs by a variety of mechanisms. Some of the receptors are G-protein-coupled receptors (GPCRs) and activate phospholipase C (PLC)-β through G protein (G). PLC cleaves PIP2 to produce IP3, which mobilizes Ca^{2+} from ER stores via IP3R Ca^{2+} release channels

Membrane Depolarization Activates Voltage-Operated Ca^{2+} Channels or Na^+–Ca^{2+} Exchanger in OPCs

OPCs express numerous ion channels, which endow them with complex physiological properties that are unique among glial population. Neuronal activity induces changes in extracellular K^+ concentration ($[K^+]_e$), which could translate neuronal activity into intracellular ion signaling in OPCs. Indeed, $[K^+]_e$ elevation to 15 mM has been shown to reduce intracellular Na^+ concentration ($[Na^+]_i$) in OPCs from 15 mM to 4.7 mM (Ballanyi and Kettenmann 1990). In parallel with the $[Na^+]_i$ changes, a $[K^+]_e$ rise can induce $[Ca^{2+}]_i$ responses through activation of voltage-operated Ca^{2+} channels (VOCCs) (Paez et al. 2009) and/or a reversal of Na^+–Ca^{2+} exchanger (NCX) (Belachew et al. 2000; Chen et al. 2007). The consequences of membrane depolarization in OPCs through these channels will be discussed below.

Voltage-Operated Ca^{2+} Channels

Six types of VOCCs (P/Q, N, L, R, and T) have been classified on the basis of electrophysiological and pharmacological properties. Chen et al. found strong, transient expression of VOCCs in CNS white matter (Chen et al. 2000). Ultrastructural analysis confirmed that VOCC immunoreactivity was located in oligodendroglial somata, projections, paranodal wraps, and loose myelin sheaths (Chen et al. 2000).

Based on the electrophysiological recording, low-voltage- and high-voltage-activated currents in OPCs from corpus callosum have been identified to possess the pharmacological and voltage-dependent properties of T-type and L-type VOCCs, respectively (Fulton et al. 2010). Meanwhile, more than 90% of the Ca^{2+} influx after plasma membrane depolarization in OPCs is mediated by L-type Ca^{2+} channels (Paez et al. 2010).

Moreover, RNA-sequencing transcriptome database of glial, neurons, and vascular cells in the cerebral cortex confirm the stage-specific expression pattern of L-type VOCCs: high level in OPCs and downregulated expressions in newly formed and myelinating oligodendrocytes (Zhang et al. 2014).

Consistent to the expression pattern of L-type Ca^{2+} channels in OPCs, studies using different pharmacological treatments to activate or block voltage-gated Ca^{2+} uptake and siRNAs to specifically knock down the L-type VOCCs in OPCs have revealed the function of voltage-gated Ca^{2+} entry on oligodendrocyte biology. For example, Paez et al. found that L-type VOCCs regulate extension/retraction of OPC processes (Paez et al. 2007). Moreover, activation of

L-type VOCC increases the amplitude of spontaneous Ca^{2+} oscillations in the soma and in the leading process of migrating OPCs, which lead to an accelerated cell migration by promoting Ca^{2+}-dependent soma translocation and leading processes formation (Paez et al. 2009). This mechanism illustrates a key role for VOCCs in the regulation of the rate of OPC migration through spontaneous Ca^{2+} oscillations.

OPCs depolarized with high K^+ displayed a more complex morphology and showed a significant increase in the expression of mature markers (Cheli et al. 2015). In contrast, L-type channel-dependent inhibitor verapamil blocks VOCC-dependent Ca^{2+} influx and significantly inhibits the morphological differentiation as well as the expression of mature oligodendrocyte markers.

In addition, studies using small interfering RNAs (siRNAs) against the Ca_v1 family of α1 subunits that conducts L-type Ca^{2+} currents suggested that OPCs lacking $Ca_v1.2$ showed decreased levels of proliferation and Ca^{2+} influx mediated by $Ca_v1.2$ channels was essential for the effect of plasma membrane depolarization on OPC development (Cheli et al. 2015).

Similar results were obtained in a recent gene knockout study, in which Cre-lox system driven by NG2 promoter was used to specifically delete L-type channel isoform $Ca_v1.2$ in OPCs (Cheli et al. 2016). Their observations indicate that L-VOCC expression can modulate OPC migration and proliferation in the postnatal brain and Ca^{2+} influx mediated by L-VOCC in OPCs is critical for normal oligodendrocyte development (Cheli et al. 2016). In addition, in a cuprizone (CPZ) model of demyelination, the adult $Ca_v1.2^{KO}$ mice showed less efficient remyelination in the brain (Santiago Gonzalez et al. 2017). Specifically, $Ca_v1.2^{KO}$ OPCs mature slower and produce less myelin than control oligodendrocytes during the recovery period after CPZ intoxication. This reduced remyelination was accompanied by a significant decline in the number of myelinating oligodendrocytes and also in the rate of OPC proliferation.

In vitro and in situ data reveal that voltage-operated Ca^{2+} influx present in OPCs and immature oligodendrocytes disappear as the cells matured. It is likely that voltage-operated Ca^{2+} influx plays a role during the first steps of OPC maturation since the expression of VOCCs decreases during development. In Cheli's work, they have established that unlike OPCs, the development of newly generated oligodendrocytes was not affected by the deletion of L-type Ca^{2+} channel (Cheli et al. 2015), indicating that there is a precise and narrow time window in which VOCCs affect OPC maturation and myelination.

Furthermore, it is hypothesized that OPC projections contacting axons sense axonal firing via the depolarization of VOCCs caused by the elevations in external K^+, ATP and glutamate that follow neuronal firing. This VOCC activation may in turn stimulate the Ca^{2+} signals that lead to myelination. It is thus plausible that the detection of axonal activity through changes in extracellular $[K^+]$, [ATP] and [glutamate] by VOCCs facilitates axon–glial signaling during the initial stages of myelin formation. These results suggest that VOCCs are important regulators of the initial stages of myelination, from process extension to the initial contact with axons.

Interestingly, in a mouse model of Timothy syndrome (TS), a gain-of-function mutation in the α1 subunit of L-VOCC $Ca_v1.2$ induces enhanced OPC development and oligodendrocyte myelination in the brain (Cheli et al. 2018). OPCs isolated from the cortex of TS mice showed greater L type Ca^{2+} influx and displayed characteristics suggestive of advanced maturation compared to control OPCs, including a more complex morphology and higher levels of myelin protein expression. Consistent with this, ectopic expression of $Ca_v1.2$ channels bearing the TS mutation in wild-type OPCs triggered process formation and promoted oligodendrocyte–neuron interaction via the activation of Ca^{2+}/calmodulin-dependent protein kinase II (Cheli et al. 2018).

The presence of voltage-gated Ca^{2+} channels in OPCs is particularly interesting, as they could directly link depolarization from synaptic activity to Ca^{2+}-triggered changes in oligodendrocyte behavior. Calcium influx through voltage gated Ca^{2+} channels modulates nearly every aspect of oligodendrocyte biology and thus may help guide successful therapeutic interventions aimed at promoting oligodendrocyte production and myelination.

Na^+–Ca^{2+} Exchanger

As an electrogenic antiporter, NCX exchanges three Na^+ for one Ca^{2+} ion, and the direction of its operation depends on Ca^{2+} and Na^+ transmembrane gradients as well as membrane potential. NCX has been revealed to be crucial for myelination. Loss of NCX3 by genetic knock-out was reported to reduce myelin protein synthesis in OPC cultures, and $NCX3^{KO}$ mice show marked hypomyelination in spinal cord (Boscia et al. 2012).

Friess and colleagues showed that developmental dynamics of intracellular ion can influence myelin basic protein (MBP) synthesis in OPCs. $[Na^+]_i$ and $[Ca^{2+}]_i$ in OPCs from cultures and callosal slices revealed significant alterations at the stage of MBP synthesis, which depends on the activity of NCX (Friess et al. 2016). At 4 days in vitro, elevated $[K^+]_e$ induces an increase of $[Ca^{2+}]_i$ levels and then stimulates MBP synthesis. A similar facilitation of MBP synthesis can be induced by partial inhibition of Na^+, K^+-ATPase (NKA) with ouabain. Blockade of NCX eliminates both $[K^+]_e$—and ouabain-induced MBP synthesis—which indicated that local $[Na^+]_i$ and/or membrane potential changes can induce NCX-mediated $[Ca^{2+}]_i$ transients and in turn affect the MBP expression (Friess et al. 2016).

Activation of Ligand-Gated and/or Neurotransmitter Receptors Controls Cytoplasm Calcium Dynamics in the Development of Oligodendrocyte

OPCs express numerous neurotransmitter receptors and ion channels, which allow them to detect products released by active neurons and endow them with complex physiological properties that is unique among glial population (Butt 2006). For example, OPC express receptors for glutamate (Bergles et al. 2000), GABA (Lin and Bergles 2004) and ATP (Hamilton et al. 2010). Here we explore the ways by which neurotransmitter can elevate intracellular calcium in OPCs.

Glutamate Mediated Calcium Entry in OPCs

NMDA Receptors

OPCs express ionotropic *N*-methyl-D-aspartate (NMDA) receptors, which are calcium-permeable. But NMDA receptor-dependent calcium transients can only be detected in a small proportion of OPCs (~20%), and NMDA receptors do not contribute to neuronal activity-evoked synaptic currents in OPCs (Hamilton et al. 2010). However, blocking NMDA receptors during oligodendrogenesis in vitro inhibits the local translation of myelin basic protein (Wake et al. 2011), and the growth factors neuregulin and brain derived neurotrophic factor (BDNF) can activate a “switch” so that myelination is highly dependent on both neuronal activity and NMDA receptors (Lundgaard et al. 2013). Consequently, the importance of NMDA receptors for calcium signaling in OPCs remains further investigation.

AMPA Receptor

OPCs express both calcium-impermeable and calcium-permeable AMPA receptors, making it possible for glutamate to increase intracellular calcium levels directly, via the opening of calcium permeable receptors, or indirectly, as AMPA receptor-mediated sodium ion entry might sufficiently depolarize OPCs to activate VOCCs. It has been shown that AMPA receptor activation can increase the amplitude and frequency of calcium transients in OPCs by a mechanism that involves the formation of a protein complex containing calcium-impermeable AMPA receptors, αv integrin and myelin proteolipid protein (Harlow et al. 2015). Therefore, a clear link exists between AMPA receptor signaling and elevated intracellular calcium in OPCs. Deng et al. have suggested that aberrantly enhanced activation of Ca^{2+}-permeable AMPA/kainite receptors may be a major mechanism in acute and repeated hypoxic-ischemic injury to OPCs in disorders of developing cerebral white matter (Deng et al. 2003). However, the role of calcium signaling in transducing the AMPA receptor signal to, for example, increase the migration velocity of OPCs (Harlow et al. 2015), or promote OPC maturation and axon remyelination after a demyelinating lesion (Gautier et al. 2015), remains to be elucidated.

Metabotropic Glutamate Receptors

Studies using RT-PCR, immunohistochemistry, and Western blot have shown that cultured OPCs express group I (mGluR1 and mGluR5), group II (mGluR3), and group III (mGluR4) metabotropic glutamate receptors (Luyt et al. 2003, 2006; Spampinato et al. 2014). As revealed in RNA-seq transcriptome study, the most highly expressed mGluR subunits are mGluR5, mGluR3, and mGluR4 (Zhang et al. 2014). These receptors are G-protein-coupled receptors (GPCRs) that couple to the $G\alpha_q$-subtype of G protein. Activation of these receptors will enable phospholipase C (PLC), which catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and diacylglycerol. IP3 then activates IP3 receptors on the endoplasmic reticulum (ER), triggering a large efflux of calcium from the ER into the cytoplasm (Niswender and Conn 2010).

Functional studies have focused mainly on group I mGluRs. In brain slices, the specific group I mGluR agonist 3,5-DHPG induces Ca^{2+} increases without accompanying current responses in hippocampal OPCs, and this response is blocked by preincubation with the mGluR antagonist LY341495 (Haberlandt et al. 2011). The use of subunit-specific antagonists 3-MATILDA and MPEP revealed that the expressions of mGluR1 and mGluR5 vary among individual OPCs. Similar results had been previously observed in cultured OPCs (Luyt et al. 2003).

Activation of group I mGluRs and subsequent elevation of intracellular Ca^{2+} in OPCs have been implicated in promoting cell survival (Luyt et al. 2006) and in inducing plasticity of neuron–OPC synapses (Zonouzi et al. 2011). In particular, treatment with 3,5-DHPG leads to an increase in the single-channel conductance of AMPARs and the proportion of calcium-permeable AMPARs in cultured OPCs. Such a mechanism may underlie the LTP-like synaptic potentiation that is observed at neuron–OPC synapses in the hippocampus (Ge et al. 2006). In addition, activation of mGluR4, a group III mGluR, with the agonist L-AP4 was shown to accelerate the differentiation of cultured OPCs (Spampinato et al. 2014). Although in vivo studies to confirm these findings have not been performed, these results point to an important role for mGluRs in regulating OPC development and synaptic plasticity.

GABA-Mediated Calcium Entry in OPCs

OPCs express ionotropic, chloride permeable, $GABA_A$ receptors, and metabotropic $G\alpha_{i/o}$-coupled $GABA_B$ receptors (Lin and Bergles 2004; Luyt et al. 2007). OPCs have a hyperpolarized resting membrane potential (approx. − 80 mV) and a high reversal potential for chloride ions relative to mature neurons (Lin and Bergles 2004), indicating that opening $GABA_A$ receptors on the OPC membrane results in an efflux of chloride ions which can depolarize the OPC membrane. If this depolarization is sufficient to activate VOCCs, this may account for the observed GABA-mediated calcium entry (Haberlandt et al. 2011). Stimulating GABAergic interneurons in the hippocampus has been shown to evoke calcium transients in OPCs (Haberlandt et al. 2011) and increasing the extracellular concentration of GABA in vivo, by inhibiting its reuptake or degradation, decreases OPC proliferation and increases oligodendrocyte production, while inhibiting $GABA_A$ receptors have the opposite effect (Zonouzi et al. 2015). However, the effect of $GABA_B$ receptors on OPC calcium signaling has not yet been examined.

ATP-Mediated Calcium Entry in OPCs

ATP acts via two different families of receptors, the ionotropic $P2_X$ receptors and the metabotropic $G\alpha_q$-coupled P2Y receptors (Hamilton et al. 2010). Also, ATP can be rapidly hydrolyzed to adenosine; therefore, the OPC's calcium response to ATP may, in part, be mediated by the activation of A1 and A3 adenosine receptors (P1 receptor) (Stevens et al. 2002).

Expression of $P2_X1$–$P2_X4$, $P2_X7$, $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptors has been demonstrated in OPCs (Agresti et al. 2005a, b). OPCs in culture and in situ respond to ATP with intracellular Ca^{2+} elevations (Agresti et al. 2005a; Hamilton et al. 2010). These elevations are not affected by changes in the external Ca^{2+} concentration but sensitive to depletion of internal Ca^{2+} stores, indicating the critical role of $G\alpha_q$-coupled P2Y receptors in responding ATP stimulation (Kirischuk et al. 1995). Meanwhile, application of specific agonists and antagonists indicated that $P2Y_1$ and $P2_X7$ receptors are major contributors in the process of Ca^{2+} elevation induced by ATP, and activation of P2Y1 promotes OPC migration and inhibits their proliferation (Agresti et al. 2005a, b).

Other Neurotransmitters Mediated Calcium Signaling in OPCs

Acetylcholine Receptors

Muscarinic acetylcholine receptors (mAChRs) are metabotropic G-protein-coupled receptors. There are five subtypes, designated M_1–M_5. M_1, M_3, and M_5 signal through the G_q protein, resulting in intracellular Ca^{2+} elevation, while M_2 and M_4 signal through the $G_{i/o}$ protein, resulting in inhibition of cAMP production. A series of studies demonstrated that acetylcholine analog carbachol induces IP3 generation, causes elevation of intracellular Ca^{2+}, induces c-fos expression, and ultimately promotes cell survival and proliferation (Cohen and Almazan 1994; Cui et al. 2006; Cohen et al. 1996; Larocca and Almazan 1997). All these effects can be blocked by atropine, a nonspecific mAChR antagonist.

Recent evidence for the functional importance of mAChRs in OPCs comes from several high-throughput screening studies aimed at identifying therapeutic targets in demyelinating disorders. Benztropine, an antagonist of M_1 and M_3 receptors, strongly promoted expression of myelin basic protein (MBP) in differentiating OPCs, and was effective at enhancing remyelination and reducing clinical severity in several animal models of multiple sclerosis (Deshmukh et al. 2013).

Glycine Receptors

Glycine receptors (GlyRs) are ionotropic receptors composed of five homo- or herteromerically assembled subunits. GlyRs conduct Cl^- and are known to be mediators of synaptic inhibition in the brain stem and spinal cord (Lynch 2009). Application of glycine has been shown to induce an inward current and Ca^{2+} elevation in cultured cortical OPCs, and these responses were inhibited by the GlyR antagonist strychnine and the Cl^- channel blocker picrotoxin (Belachew et al. 1998, 2000). However, the function of glycine in oligodendrocyte biology remains to be explored.

Serotonin Receptors

There are seven subtypes of serotonin receptors, $5\text{-}HT_1$–$5\text{-}HT_7$. Other than $5\text{-}HT_3$, which is ionotropic, all are metabotropic G-protein-coupled receptors. In OPC cultures, intracellular Ca^{2+} elevation was detected in response to serotonin, and chronic serotonin or $5\text{-}HT_{2A}$ receptor agonist administration reduced OPC differentiation and inhibited myelination of axons in neuron–oligodendrocyte co-cultures (Fan et al. 2015). Although $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors express throughout the oligodendrocyte lineage in culture (Fan et al. 2015), there have been no analyses of the in vivo expression of serotonin receptors in OPCs.

Intracellular Ca^{2+} Signaling in OPCs

It is known that endoplasmic reticulum (ER) is the major intracellular Ca^{2+} pool and that ER Ca^{2+} release is driven mainly by inositol-1,4,5,-trisphosphate receptors (IP_3Rs) and ryanodine receptors (RyRs) (Koulen and Thrower 2001). G-protein-coupled receptors (GPCRs) activating phospholipase Cβ (PLCβ) and tyrosine-kinase receptors (TKR) activating PLCγ cleave phosphatidylinositol 4,5 bisphosphate (PIP_2) into IP_3 and diacylglycerol (DAG). IP_3 binding to IP_3R allows the diffusion of Ca^{2+} from ER to increase intracellular $[Ca^{2+}]$ from ~ 100 nM to ~ 1 μM for many seconds. Different from IP_3Rs, RyRs are Ca^{2+}-induced Ca^{2+} release (CICR) channels that is triggered merely by a low concentration of Ca^{2+} (~ 1 μM) (Meissner 1986; Bezprozvanny et al. 1991), and this CICR function has been shown to powerfully amplify small inward Ca^{2+} currents in NG2 glial cells (Haberlandt et al. 2011).

Compared to the extensive studies on VOCCs, the function of intracellular Ca^{2+} channel on the differentiation of OPCs remains largely elusive. In a recent research by Li and colleagues (Li et al. 2018), RyR3 has been identified as the only isoform that selectively expressed in oligodendrocyte, and strong RyR3-positive signal was found distributed all over the cytoplasm and processes in OPCs and/or immature OLs (imOLs). However, the expression of RyR3 gradually decreased in mature oligodendrocytes and was located mainly around the perinuclear region. In addition, RyR3-mediated intracellular Ca^{2+} waves following caffeine stimulation were correlated with the expression pattern of RyR3, in which high flat Ca^{2+} fluctuations and oscillatory Ca^{2+} waves were more frequently recorded in OPCs and imOLs than in OLs. Moreover, inhibiting the function of RyR3 either pharmacologically or by gene knockdown could neutralize the increased intracellular Ca^{2+} and suppress OPC differentiation (Li et al. 2018). These observations indicate that RyR3 is likely a critical bridge for the formation of intracellular Ca^{2+} signaling and thus, it participates in the regulation of oligodendroglial development.

In OPCs, both IP_3R2 and RyR3 can mediate highly localized Ca^{2+} release, of the types called ''puffs'' and ''sparks'', respectively (Haak et al. 2001). But only IP_3R2 is able to initiate Ca^{2+} waves under pharmacological treatments (Haak et al. 2001). IP_3R2, also called Itpr2, has been identified as a distinct marker for postmitotic oligodendrocyte subclass (Marques et al. 2016; Zeisel et al. 2015). Therefore, it will be interesting to understand the contribution of IP_3R2 mediated Ca^{2+} signaling in oligodendrocyte biology.

Preferential Myelination of Electrically Active Axons is Mediated Through Local Ca^{2+} Increase in Oligodendrocyte

Since mature oligodendrocytes can be associated with axons early in development but not forming myelin until much later in prenatal or adult life (Back et al. 2002), it is hypothesized that signals from axons must also regulate initiation of myelin wrapping even after OPCs have matured. In vitro studies have shown that vesicular release of glutamate from axons can stimulate local translation of MBP and induce preferential myelination on electrically active axons (Wake et al. 2011, 2015), which is stimulated by local rise of cytoplasmic calcium in glial cell processes (Wake et al. 2015).

Although there are several recent studies presented in vivo data suggesting the critical role for local Ca^{2+} transients and waves in regulating myelination, the contribution of neuronal activity on myelination has not been fully understood. An live-imaging study in zebrafish revealed distinct signatures of localized Ca^{2+} activity during CNS myelination (Baraban et al. 2018). High-amplitude, long-duration Ca^{2+} transients preceded localized retraction of sheaths, mediated by calpain, whereas the frequency of lower-amplitude, shorter duration transients in stabilized sheaths correlated positively with their speed of elongation. Another study using the similar model demonstrated that approximately half of the $[Ca^{2+}]_i$ transients in developing oligodendrocytes are driven by axonal action potentials, as they are blocked by TTX and their rate is increased by electrical stimulation (Krasnow et al. 2018). The remainder of the transients occur spontaneously, perhaps by TRPA1 channels in oligodendrocyte sheaths (Shigetomi et al. 2011; Hamilton et al. 2016). In addition, the authors revealed that lengthening of the myelin sheath is driven by the rate of $[Ca^{2+}]_i$ transients occurring and, below a certain rate, sheaths shorten, so a minimum $[Ca^{2+}]_i$ transient rate are required to maintain sheath length (Krasnow et al. 2018). However, long-duration $[Ca^{2+}]_i$ bursts imparting a high calcium load were also associated with shortening. These results suggest that modest $[Ca^{2+}]_i$ elevations trigger sheath elongation, while very low or excessively large rises lead to sheath shortening.

Interestingly, a recent study using one-photon Ca^{2+} imaging, discovered that myelin microdomain calcium transients are generated by the spontaneous activity of mitochondria in the noncompacted myelin, independently from neuronal activity (Battefeld et al. 2019). This observation suggested whether myelin Ca^{2+} activity differs between OL population and how these are linked with differential activity dependence of myelination remains to be established.

Conclusion and Further Perspectives

Oligodendrocytes at different developmental stages are diverse in their morphological features and gene-expression profiles, and in many cases, also in their expression of specific regulators of the calcium signal. Neuronal activity is a major external signal controlling CNS myelination throughout life (de Faria et al. 2019); neurotransmitters, or other signaling molecules released in response to neuronal activity, evoke transient increases in intracellular calcium in

Table 1 Effects of multiple calcium channels on oligodendrocyte biology

Channel type	Channel name	Agonist	Antagonist	Effects in oligodendrocyte	References
Membrane depolarization-dependent receptor/exchanger	VOCC	Bay K 8644	Verapamil, nifedipine; ω-agatoxin, ω-conotoxin	Accelerate OPC migration, proliferation, and myelination	Paze et al. (2009), Cheli et al. (2015, 2016)
	NCX		SEA0400, ORM-10962	Stimulate MBP synthesis	Boscia et al. (2012), Friess et al. (2016)
Ligand-gated receptor	NMDAR	Aspartic acid	Ketamine, APV, dextromethorphan hydrobromide	Activate myelination for unknown mechanism	Lundgaard et al. (2013)
	AMPAR	(*RS*)-AMPA hydrobromide	NBQX, DNQX	Unknown	Harlow et al. (2015)
	mGluR	3,5-DHPG, L-AP4	LY341495, 3-MATILDA, MPEP	Promote cell survival and accelerate OPC differentiation	Luyt et al. (2006), Spampinato et al. (2014)
	GABA_A receptor	GABA, THIP hydrochloride	(−)-Bicuculline methiodide, Picrotoxin	Decrease OPC proliferation and increase oligodendrocyte production for unknown mechanism	Zonouzi et al. (2015)
	P2X, P2Y	ATP	*Iso*-PPADS tetrasodium salt, MRS 2279, MRS 2179	Promote OPC migration and inhibit proliferation	Agresti et al. (2005a, b)
Neurotransmitter receptors	mAChR	Arecoline hydrochloride, cevimeline hydrochloride hemihydrate	Atropine, solifenacin hydrochloride, tolterodine tartrate, benzetimide hydrochloride	Modulate the expression of MBP and remyelination	Deshmukh et al. (2013)
	GlyR	L-Alanine, taurine, β-aminobutyric acid	Strychnine, PMBA	Unknown	Belachew et al. (2000)
	Serotonin receptor	Triptans; azapirones; BRL-54443	Ketanserin, cyproheptadine	Reduce OPC differentiation and inhibit myelination	Fan et al. (2015)
Intracellular Ca^{2+} signalling	RyR	Caffeine, 4-chloro-m-cresol	Dantrolene	Promote OPC differentiation	Li et al. (2018)
	IP3R	Adenophostin A, ribophostin	Xestospongin, 2-APB	Unknown	Haak et al. (2001)

VOCC voltage-operated Ca2+ channel, *NCX* Na+–Ca2+ exchanger, *NMDAR N*-methyl-D-aspartate receptor, *AMPAR* α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor, *mGluR* metabotropic glutamate receptor, *GABA* γ-aminobutyric acid, *mAChR* muscarinic acetylcholine receptor, *GlyR* glycine receptor, *RyR* ryanodine receptor, *IP3R* inositol-1,4,5,-trisphosphate receptor

oligodendrocyte progenitor cells. The fact that OPCs have synapses and express an array of neurotransmitter receptors makes them well equipped to interpret and differentially respond to distinct activity patterns. The contribution of different calcium channels in the regulation of oligodendrocyte differentiation is summarized in Table 1. Calcium signaling modulates nearly every step of oligodendrocyte development in the brain, and the development of new tools including genetically encoded Ca^{2+} indicators has transformed our understanding of how Ca^{2+} signals are generated, compartmentalized, and dissipated during these processes.

The largest area of uncertainty perhaps relates to how calcium dynamics cooperate with transcriptional regulators in OPCs, and how aberrant function of particular Ca^{2+} channels in oligodendrocyte affects the cross-talk between oligodendrocytes and neurons. A recent study identified that as sensors of intracellular calcium concentrations, calcineurin signaling and its Nfat effector are instrumental in resolving cross-repressions of Olig2 and Nkx2.2 as Sox10 partners during the maturation of oligodendrocyte (Weider et al. 2018). Thus, Nfat proteins confer a means of linking extrinsic and intrinsic regulations of oligodendroglial differentiation and myelination.

Besides, calcium signals have been suggested to be involved in oligodendrocyte-related diseases. For example, changes in Ca^{2+} dynamics during secondary degeneration have been shown to be associated with oxidative stress and disruptions to myelin structure (Wells et al. 2012). In partial optic nerve transection injury model, in vivo administration of three ion channel inhibitors for VGCCs, P2X7Rs, and AMPARs in combination significantly prevented OPC loss in acute phase (O'Hare Doig et al. 2017) and preserved myelin compaction in chronic phase (Savigni et al. 2013). In an experimental autoimmune encephalomyelitis (EAE) model for Multiple Sclerosis, application of inhibitors for N-type VGCC/TRPA1-mediated calcium influx, CTK 01512-2, displayed a favorable profile on EAE-induced neuroinflammatory changes, including inflammatory infiltrate and demyelination (Silva et al. 2018). Although the responding cell types have not been elucidated in these studies, the existence of multiple routes of Ca^{2+} influx opens the possibility that the activity of calcium channels can be manipulated pharmacologically to encourage oligodendrocyte maturation and remyelination after demyelinating episodes in the brain.

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Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest for any of the authors.

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