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REVIEW

Oligodendroglial GABAergic Signaling: More Than Inhibition!

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Abstract GABA is the main inhibitory neurotransmitter in the CNS acting at two distinct types of receptor: ligand-gated ionotropic $GABA_A$ receptors and G protein-coupled metabotropic $GABA_B$ receptors, thus mediating fast and slow inhibition of excitability at central synapses. GABAergic signal transmission has been intensively studied in neurons in contrast to oligodendrocytes and their precursors (OPCs), although the latter express both types of GABA receptor. Recent studies focusing on interneuron myelination and interneuron-OPC synapses have shed light on the importance of GABA signaling in the oligodendrocyte lineage. In this review, we start with a short summary on GABA itself and neuronal GABAergic signaling. Then, we elaborate on the physiological role of GABA receptors within the oligodendrocyte lineage and conclude with a description of these receptors as putative targets in treatments of CNS diseases.

Keywords GABA · $GABA_A$ receptor · $GABA_B$ receptor · OPC · Oligodendrocyte lineage

Introduction

GABA (γ-aminobutyric acid), besides glycine, is the main inhibitory neurotransmitter in the central nervous system (CNS) [1]. The existence of GABA in the brain was first detected in 1950 [2], without knowing its biological function. Seven years later, studies found that GABA was the "I factor", the inhibitory neurotransmitter of the mammalian CNS [3]. Thereafter, GABA and GABAergic signaling on neurons were extensively studied [1]. GABA binds to two classes of receptor in the CNS, $GABA_A$ and $GABA_B$ receptors, and exerts fast or slow inhibition at synaptic terminals. Decades later, since 1978 [4], glial GABA signaling started to attract interest and is now a major research focus while new roles of glial cells are emerging. Oligodendrocytes (OLs) are the myelinating cells of CNS making them indispensable for fast and efficient action potential conduction. They differentiate from precursor cells (OPCs) [5–8]. Despite lifelong ongoing differentiation into OLs, OPCs maintain a certain cell density due to continuous self-renewal [9–12]. Proliferation and differentiation of OPCs are modulated by growth factors [13–15], as well as by communication between OPCs and axons [16–18]. OPCs are the only glial cells receiving direct synaptic input mediated by glutamate and GABA from excitatory and inhibitory synapses, respectively [17, 19–23]. Furthermore, the myelination of interneurons by mature OLs appears to be a direct consequence of GABA-based interneuron-OPC communication [24–26].

GABA Synthesis, Release, and Uptake in the Brain

GABA availability in the CNS is either ensured by synthesis from glutamate by the glutamic acid decarboxylase enzymes (GAD) 67 and GAD65 [27, 28] or by monoacetylation of putrescine [29, 30]. Synthesis by GADs in the glutamine-glutamate cycle (GGC) is the most common pathway and GABA level are mostly determined by the activity of GADs. Briefly, in the GGC, glutamate is

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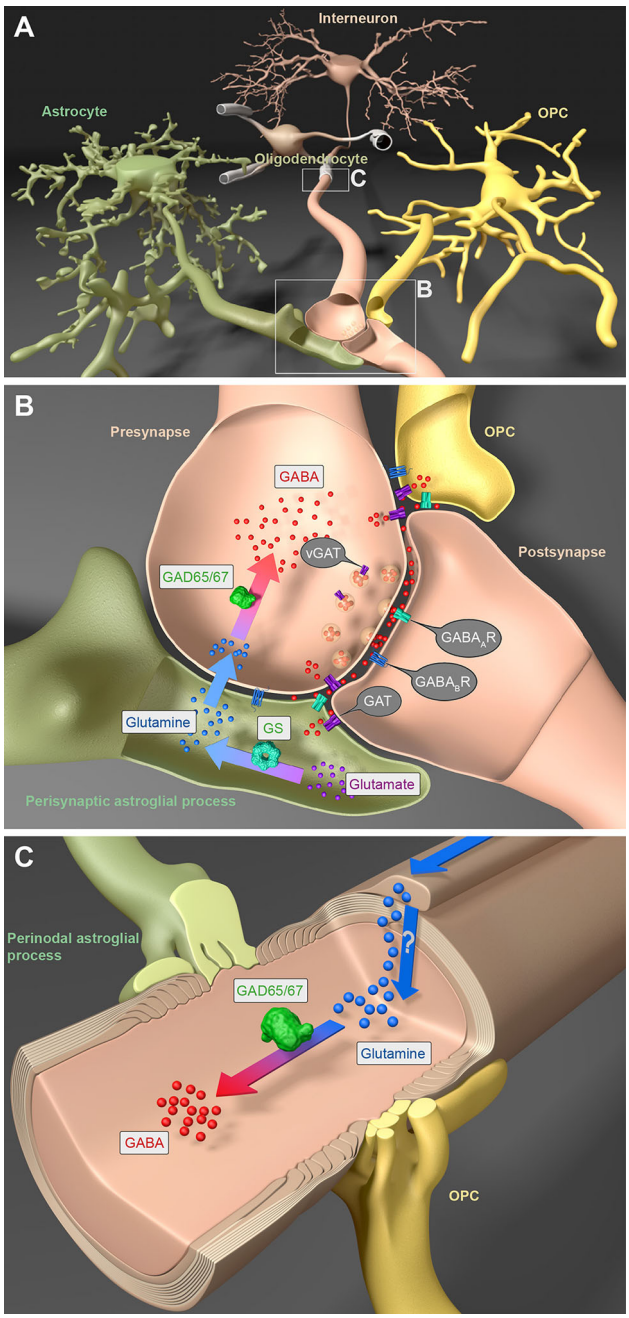

Fig. 1 GABA cycling between interneurons, cells of the oligodendrocyte (OL) lineage, and astrocytes. **A** In the central nervous system, interneurons form an intricate signaling network with cells of the OL lineage, i.e., myelinating OLs and their precursors (OPCs), and with perisynaptic as well as perinodal processes of astrocytes. **B** In the synaptic microenvironment, extracellular glutamate is converted into glutamine in astrocytes by glutamine synthetase (GS). After release, glutamine is taken up by interneurons and transformed into GABA by the glutamate decarboxylases GAD65 and/or GAD67. Upon action potential arrival, GABA is released into the synaptic cleft by vesicles expressing GABA transporters (vGAT). After binding to postsynaptic neuronal $GABA_A$ and/or $GABA_B$ receptors, GABA induces postsynaptic neuronal hyperpolarization. But neuron-released GABA can also act on the GABA receptors of OPCs modulating axonal myelination. In addition, extrasynaptic GABA is taken up by neuronal GAT1 and astroglial GAT3 transporters. Both transporters, however, are also expressed by OPCs, but functional studies are still required to determine their roles. **C** Also, OLs can express GS to produce glutamine. The latter might be transported to myelinated axons, where it can be converted into GABA. Additional experiments are still required to test this hypothesis.

transformed into glutamine by glutamine synthetase of astrocytes (Fig. 1A, B). Glutamine is released by several types of glutamine transporter and taken up by neurons, where it is converted into glutamate. The latter is finally processed by GADs to produce GABA in GABAergic neurons [31] (Fig. 1B). Although GAD67 and GAD65 share a large similarity of their genes (*GAD1* and *GAD2*, respectively), their expression pattern and functions are quite disparate. GAD67 is uniformly distributed in the whole cell while GAD65 is mainly found in the axonal terminals [32]. In addition, GAD67 is already expressed during early development while GAD65 is more prominent in later stages (reviewed by [27]). These spatial and temporal differences are highly related to their functions. GABA produced by GAD67 mainly functions as a neurotrophic factor and is independent of neurotransmission, e.g., involved in synaptogenesis during development (reviewed by [27]). GAD65, however, is responsible for synaptic neurotransmission. Therefore, it is not surprising that GAD67-null mice cannot survive longer than a day after birth, while GAD65-null mice are born with slowly developing spontaneous seizures [33, 34]. Although these deficits are highly likely attributable to disordered neuronal GABA synthesis, the GABA contribution from glial cells must not be neglected. GAD65 and GAD67 are both expressed in glial cells [35]. Astrocytes of the olfactory bulb, hippocampus, thalamus, and cerebellum (i.e., Bergmann glia) release GABA to inhibit neighboring neuronal activity [36–39]. Recently, GAD65/67 and monoamine oxidase B, as well as GABA were found in OPCs and oligodendrocytes *in vitro* [40]. These findings suggest the potential of autocrine or paracrine GABAergic signaling pathways for oligodendrocyte (OL) development and/or neural circuit formation. Besides astrocytes, OLs also express glutamine synthetase in caudal regions and the spinal cord [41], providing a potential source of glutamine for axons *via* myelin-axon communication (Fig. 1A, C). In the case of inhibitory axons, glutamine is further transformed into GABA (Fig. 1C). More studies are required to confirm the functional GABA synthesis, release, and uptake in cells of the OL lineage.

GABA-containing transmitter vesicles (vGAT) are filled in synaptic terminals (Fig. 1B) and released in a Ca^{2+}-dependent manner. The general mechanism of vesicular exocytosis, membrane fusion, and release of anchored GABA vesicles is triggered by Ca^{2+} influx through

voltage-gated Ca^{2+} channels (VGCCs). In addition, GABA can reach the extracellular space *via* reversal of GABA transporters (GATs), called non-vesicular release [42–44]. Previously, GATs were mainly considered to be responsible for GABA uptake from the synaptic cleft. For this GABA uptake, GATs utilize the chemical Na^+ gradient, aided by a Cl^- gradient; e.g., neuronal GAT1 co-transports two Na^+ and one Cl^- together with one GABA molecule. This transport not only increases the intracellular levels of GABA, Na^+, and Cl^-, it also depolarizes the neuron. Under baseline conditions, GATs operate near equilibrium [43]. Therefore, upon moderate depolarization evoked by a short series of action potentials, transporter reversal occurs [45, 46]. However, during excessive network activity and enhanced synaptic GABA release, elevated levels of extracellular GABA favor GABA uptake by GATs [47]. Therefore, how the operation of GATs, including their reversal, is exactly controlled and how this process is related to physiological functions is yet unclear.

As a very complex but highly precise organ, our brain keeps a balance of excitatory and inhibitory signals to control proper behavioral performance. As reported, both vGAT-null (little, if any, GABA release) [48] and GAT1-null (no GABA clearance) mice cannot survive beyond birth [49]. Therefore, it is critical to maintain GABA homeostasis in the extracellular space by synchronized regulation of GABA release and uptake. In the brain, two different GATs fine-tune the neuronal excitability: GAT1 (*SLC6A1*) on presynaptic terminals and GAT3 (*SLC6A11*) on perisynaptic astroglial processes (Fig. 1B). Transcriptome studies have revealed that astroglial GAT3 dominates over GAT1. In addition to neurons, OPCs and OLs express functional GAT1, though at rather low levels [35, 40, 50] (Fig. 1B). However, functional studies demonstrating the biological impact of GAT1 for cells of the OL lineage are still missing. In addition to GAT1 and 3, some GAT2 (*SLC6A13*) immunoreactivity has been observed on CNS blood vessels [51]. GAT2 mainly permits efflux of GABA and taurine from the brain to the circulating blood stream [51]. Therefore, GAT2-deficient mice have slightly increased taurine in the brain [52]; however, they perform normally under physiological conditions. Transcriptome data suggest GAT2 expression by OPCs, though at a low level. This is interesting in respect to the current notion that OPCs can also contribute to the blood-brain barrier (BBB) while migrating along blood vessels during development [53]. Taken together, these findings suggest a potential novel function of OPCs in neural circuits, by either taking up GABA from extracellular space or by being associated with the overall GABA efflux through the BBB to the periphery. Nevertheless, more functional studies are required to identify the role of GAT2 in OPCs. In juvenile rats, GAT1 and GAT3 have also been detected in OLs [40], however, it is yet elusive whether and how both GATs function in OL GABA circulation.

GABA Receptors and Their Biological Actions on Neurons

To exert inhibition, GABA binds to two distinct receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are ligand-gated ionotropic transmembrane receptors, permeating Cl^- ions in both directions [54]. To date, a plethora of 19 $GABA_A$ receptor subunits have been identified in the mammalian CNS: α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3 [55]. In general, the pentameric receptor assembly is composed of two α, two β and one γ subunit (Fig. 2A, B). Due to various subunit compositions and distinct regional distributions, $GABA_A$ receptors exhibit tremendous diversity in terms of biophysical properties and dynamic regulation [55, 56]. Since the subunits ρ1–3 form complexes with themselves only, and not with other subunits, they are designated as $GABA_C$ or $GABA_{A\text{-}\rho}$ receptors. However, they are similar to $GABA_A$ receptors in structure, function, and mechanism of action [57].

The $GABA_A$ receptor is permeable to Cl^- anions in both directions depending on the difference between extra- and intracellular Cl^- concentrations. In general, extracellular Cl^- is above its equilibrium potential. Therefore, upon postsynaptic $GABA_A$ receptor activation, a fast Cl^- influx generates neuronal hyperpolarization. This raises the threshold for postsynaptic action potentials and thereby decreases excitatory neurotransmitter release, i.e., inhibitory neurotransmission [58, 59] (Fig. 2A). Notably, $GABA_A$ receptors are also expressed at extra-synaptic regions. These receptors can be activated by GABA spillover, leading to tonic inhibition [55].

$GABA_B$ receptors are metabotropic G-protein-coupled receptors. Two major $GABA_B$ receptor isoforms ($GABA_{B1}$ and $GABA_{B2}$) and various splice variants ($GABA_{B1a\text{–}g}$) have been described [60, 61]. $GABA_{B1}$ and $GABA_{B2}$ are co-expressed, generating functional receptors in a heterodimeric assembly [62–64], although some functional homodimers have been described as well [65]. The ligand-binding B1 subunit remains in the endoplasmic reticulum through a retention signal until assembly with the B2 subunit [66]. Only the assembled receptor dimers reach the cell surface and function. GABA activation occurs *via* a Venus flytrap domain of the B1 subunit [60, 67].

Neuronal $GABA_B$ receptors are located in both pre- and postsynaptic membranes. Its G protein activation triggers dissociation of G_α and $G_{\beta\gamma}$ subunits. Binding of $G_{\beta\gamma}$ to VGCCs leads to reduced presynaptic Ca^{2+} influx preventing vesicular release (Fig. 2A) [68, 69], while decreased postsynaptic Ca^{2+} current suppresses neuronal excitability

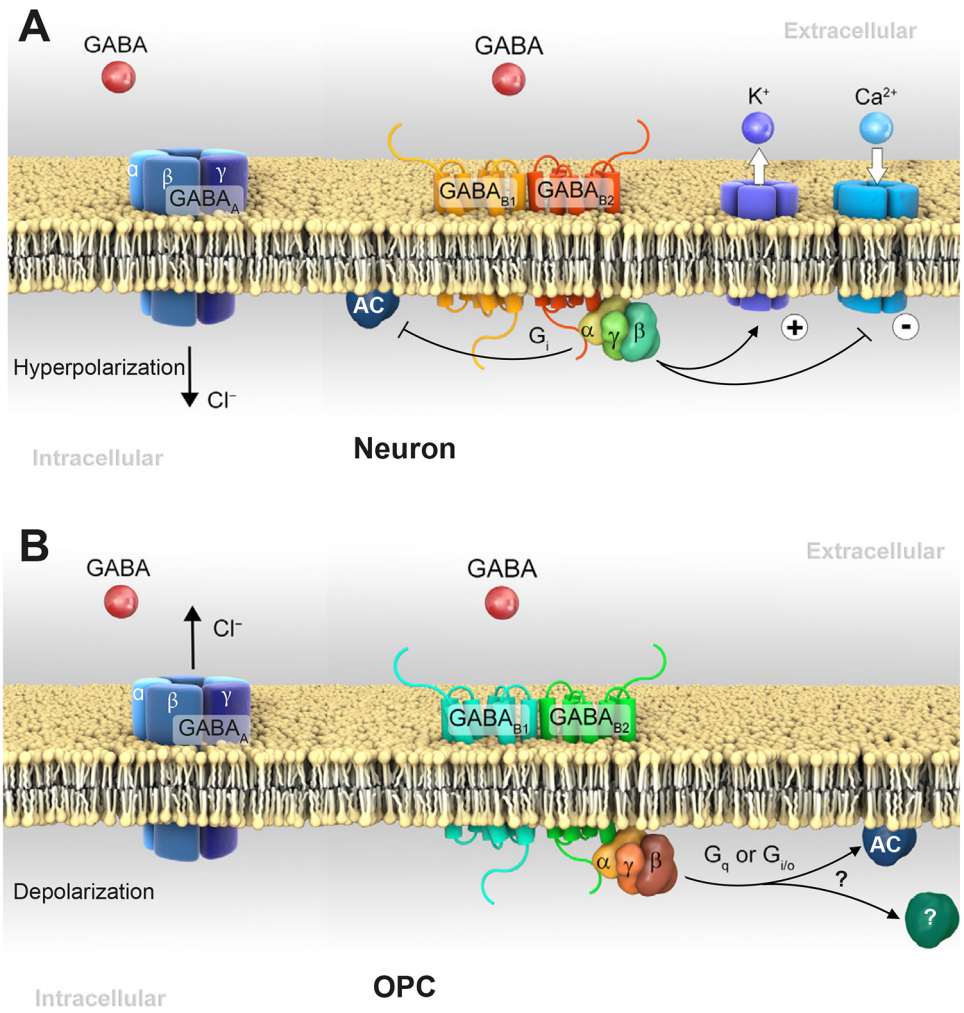

Fig. 2 GABA receptor expression in neurons and OPCs. **A** Activation of ionotropic $GABA_A$ receptors induces Cl^- influx to hyperpolarize neurons. The $GABA_{B1}$ subunit confers ligand-binding, while the B2 subunit transduces the GABA signal into the cell. Activation of the neuronal $GABA_B$ receptor induces dissociation of G_α and $G_{\beta\gamma}$ subunits. The G_α subunit inhibits adenylyl cyclase (AC), while $G_{\beta\gamma}$ activates G protein-gated inwardly rectifying K^+ channels and inhibits voltage-gated Ca^{2+} channels (VGCCs), thereby reducing neurotransmitter release. The regulation of VGCCs can occur pre- and postsynaptically. **B** Different from neurons, in OPCs, activation of $GABA_A$ receptors causes a Cl^- efflux and depolarization based on the higher levels of cytosolic Cl^-. $GABA_B$ receptors expressed in OPCs are thought to transduce signals *via* G_α with or without association of $G_{\beta\gamma}$; or *via* the G_q pathway linked to phospholipase C, further increasing intracellular Ca^{2+} release from the endoplasmic reticulum.

[70, 71]. In addition, postsynaptically, $G_{\alpha i/o}$ inhibits adenylyl cyclase, thereby reducing cAMP levels, while $G_{\beta\gamma}$ activates G protein-gated inwardly-rectifying K^+ channels, hyperpolarizing the postsynaptic membrane (Fig. 2A). $GABA_B$ receptors regulate gene expression by interacting with activating transcription factor 4 (ATF-4), a member of the cAMP response element-binding protein (CREB)/ATF family [60, 72, 73]. Disruption of $GABA_B$ receptor-mediated responses has been associated with several neuropathologies including epilepsy and hyperalgesia [74].

Apart from acting as an inhibitory neurotransmitter, GABA is also considered to be a neurotrophic factor. In cultured cerebellar granule cells, retinal neurons, and neuroblastoma neurons, GABA promotes neurite growth [75]. Another peculiar finding is that GABA can act as an excitatory neurotransmitter in cortical and hippocampal neurons during early postnatal days [76–78]. At this age, the Nernst potential of Cl^- is positive in respect to the resting membrane potential due to higher activity of the cation-chloride importer Na-K-Cl cotransporter in comparison to the extruder K^+-Cl^- cotransporter 2, and the opening of $GABA_A$ receptors results in Cl^- efflux with subsequent depolarization [79].

Expression of GABA Receptors in Cells of the Oligodendrocyte Lineage

Already in 1984, GABA-evoked responses were reported in a subpopulation of OLs from explant cultures of the mouse spinal cord [54]. These cells were depolarized by GABA (1 mmol/L, 4 mV depolarization). This depolarization was sensitive to competitive as well as non-competitive $GABA_A$ receptor antagonists [54]. These experiments provided the first evidence of the functional expression of $GABA_A$ receptors in OLs. A follow-up study on cultured OPCs and OLs further demonstrated that the GABA-induced depolarization (10^{-2} mmol/L, 30–680 pA in 60% of the OL lineage cells) was due to Cl^- efflux [80] (Fig. 2B). Also, in acutely isolated slices of corpus callosum and hippocampus, $GABA_A$ receptors evoked

depolarization in OPCs (1 mmol/L GABA, 75 pA and 324 pA, respectively) [81, 82]. Notably, $GABA_A$ receptor expression was found to be down-regulated during the lineage progression from proliferating OPCs to myelinating OLs. The current response to GABA as well as intracellular Ca^{2+} increases were drastically reduced *in situ* [80, 81, 83] and *in vitro* [84]. In line with this, recent transcriptome studies as well as single-cell qRT-PCR have shown a decrease of all $GABA_A$ receptor subunits (α1–5, β1–3, and γ1–3) through OL development [35, 85, 86]. In particular, the γ2 subunit is only expressed in OPCs and not in OLs [35, 85, 86]. Interestingly, the γ2 subunit is specifically detected at the postsynaptic OPC membranes of parvalbumin fast-spiking interneuron-OPC synapses [87], at levels comparable to neuronal postsynaptic expression [88, 89]. Of note, the γ2 subunit is required for the postsynaptic clustering of $GABA_A$ receptor subunits [88]. From postnatal week 2 to 4, the number of OPCs expressing α2, α5, β1, and γ2 is decreased while that of α3 and 4 is increased [86]. Of interest, this is the exact age when the synaptic transmission of OPCs switches to extra-synaptic communication [20]. However, the γ2 subunit does not appear to affect OPC proliferation and differentiation, which appears unperturbed in mice with conditional deletion of the γ2 subunit in OPCs [90].

While $GABA_A$ receptor levels are strongly reduced in mature OLs [35, 80, 83, 84], axonal contacts trigger the expression of α1 and α3 *in vitro* as well as *in situ* [83]. However, neuronal activity does not appear to be required, since blocking it with tetrodotoxin did not alter the OL response to GABA in neuron-OL co-cultures. It is not clear yet whether these two subunits co-assemble in the same $GABA_A$ receptor complex or whether they are components of separate and distinct receptors. Additional studies are required to address the functional role of α1 and α3, but also of other $GABA_A$ receptor subunits in OPCs and OLs.

It will be exciting to learn how the spatial-temporal pattern of each subunit, including its subcellular localization, can be correlated with distinct functions in the various subpopulations of the OL lineage. The heterogeneity of OLs, in terms of anatomical location in the brain, was already described at 1921 by del Río Hortega [91]. A century later, using the single-cell RNAseq approach, studies have provided direct evidence for and confirmed an even more complex heterogeneity of OL lineage cells [92–94]. Reconsidering the early finding that only a subpopulation of OLs respond to GABA [54], we are now confronted with numerous subgroups of OLs that may or may not express GABA receptors. And, even if they are expressed, the pentameric composition of each receptor might differ in each subgroup and result in a huge diversity of GABA responses. So far, it is too early to speculate about the exact role of each subunit.

The metabotropic GABA receptor subunits $GABA_{B1}$ and $GABA_{B2}$ are both expressed throughout the OL lineage [35], from the subventricular zone [95] to the corpus callosum [40] and spinal cord [65]. However, so far, $GABA_B$ receptors have not been detected in compact myelin structures [96]. Both B1 and B2 subunits were found to be down-regulated during OPC differentiation to OLs *in vitro* [95]. Intriguingly, the ratio of $GABA_{B1}$ to $GABA_{B2}$ also changes with the differentiation of OPCs into OLs, suggesting that B1 or B2 subunits can cooperate with other elements, even forming homodimers with novel functions as is known for some neurons [97, 98]. In the hippocampus of $GABA_{B2}$-null mice, an atypical electrophysiological $GABA_B$ response has been recorded, suggesting that $GABA_{B2}$ is not indispensable for $GABA_B$ receptor signaling [97]. In addition, several studies also reported coupling of the $GABA_{B2}$ subunit with other G-protein-coupled, heptahelical receptors. The $GABA_{B2}$ subunit is functionally paired with the M2 muscarinic receptor in cortical neurons [98]. As well, functional cooperation of $GABA_{B2}$ subunits and somatostatin receptor 4 has been found in the non-perisynaptic processes of astrocytes [99]. All these reports point to close interactions of $GABA_B$ receptor subunits with other G-protein-coupled receptors. However, additional studies are necessary to determine whether this applies to OPCs and/or OLs and if this might change with aging.

Physiological Functions of GABA Receptors in the Lineage of Oligodendrocyte

Proliferation, Differentiation, and Myelination

While the sensitivity to GABA is largely reduced in mature OLs [65, 81, 95], a pivotal role of GABA signaling has been suggested during the origin of OPCs and the initial stages of axon recognition and myelination [22, 100]. Systemic application of the $GABA_A$ receptor antagonist bicuculline drastically increased OPC proliferation while an increase of GABA evoked the opposite in cerebellar white matter [22]. In addition, endogenous GABA bisected the number of OPCs and mature OLs in organotypic slice cultures of mouse cortex, and this was reversed by the $GABA_A$ receptor blocker GABAzine [18], suggesting an inhibitory role of $GABA_A$ receptor signaling on OPC self-renewal and myelination [18]. However, it is still elusive whether this occurs by direct activation of OPC $GABA_A$ receptors or by a more complex process integrating the activation of OPC $GABA_A$ receptors and signals from a GABA-evoked neuronal response.

GABAergic signaling of the OL lineage seems to be essential for interneuron myelination. First of all, in layers

2/3 and 4 of cortex, the majority of myelinated axons are interneurons [26]. Among these, parvalbumin (PV)-positive interneurons account for a large proportion. Secondly, interneuron myelination is positively related to axonal activity and caliber [24, 25]. Considering that PV neurons are fast-spiking interneurons in the neocortex [101, 102], these studies strongly suggest a putative GABAergic communication between PV interneurons and OPCs. Indeed, a recent study revealed that disruption of PV interneuron-OPC interaction due to a loss of the γ2 subunit of $GABA_A$ receptors in OPCs results in hypomyelination of PV neurons in the barrel cortex [103]. PV-OPC synaptic structures were visualized by Tanaka *et al.* in 2009 [104]. A few years earlier, interneuron-OPC synapses were first detected in acute hippocampal slice preparations by Lin and Bergles [105]. CA1 interneurons directly release GABA, acting on the postsynaptic $GABA_A$ receptors of OPCs. These inhibitory neuron-OPC synaptic structures have been subsequently confirmed in numerous studies [20–22, 104] in both grey and white matter [20–22, 86, 87, 90, 105, 106] (Fig. 3A). In cortex, for instance, OPC synapses are ~90% inhibitory [87]. This synaptic transmission (*via* $GABA_A$ receptors) peaks at the second postnatal week (p10), and is immediately followed by a drastic increase in the OL population [20]. However, the communication pattern switches to extra-synaptic until the fourth postnatal week, when the GABAergic currents of OPCs are mainly elicited by GABA spillover. Of note, at this time point, the differentiation of cortical OLs is largely completed, further suggesting that, in the early postnatal cortex, synaptic interneuron-OPC contacts are essential for OPC differentiation and interneuron myelination. Extra-synaptic GABA level, however, could be involved in the adaptive regulation of myelination. Indeed, forced increases of GABAergic connectivity between interneurons and first-wave OPCs favor deep layer myelination in the somatosensory cortex [106]. It will be interesting to investigate whether different waves of OPCs [107] form synapses with impact on distinct neuronal network activity or other biological processes. In addition, it is important to state that GABA-mediated myelination might be very different from glutamate-based processes, as indicated by shortened nodes and internodes as well as higher myelin basic protein expression of myelinated GABAergic axons than in non-GABAergic axons [26].

To date, no direct evidence is available demonstrating a decisive role of GABAergic signaling for the development of OL lineage cells *in vivo*. *In vitro*, GABA application fails to affect primary OPC proliferation [108, 109], while selective activation of $GABA_B$ receptors with baclofen promotes the proliferation of the OPC cell line CG-4 [95]. These results further suggest the manifold roles of GABA when activating both $GABA_A$ and $GABA_B$ receptors leading to a complex series of events. However, the

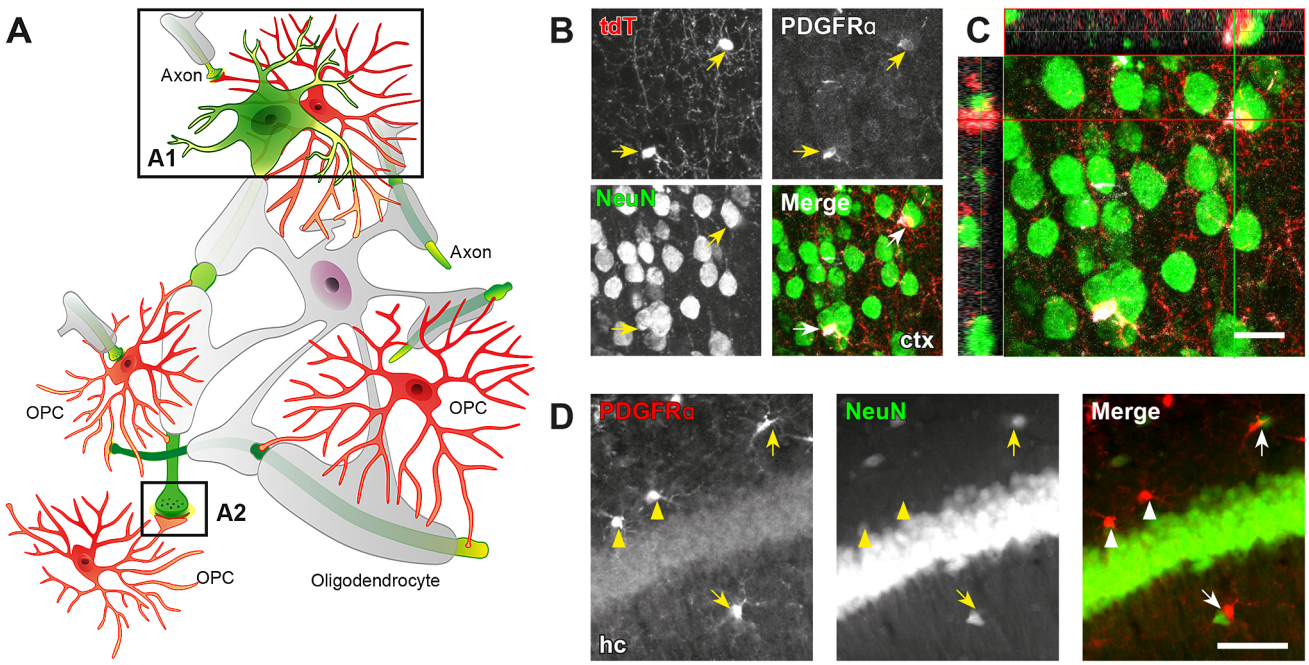

Fig. 3 Synaptic and non-synaptic neuron-OPC communication. **A** Schematic of neuron-OPC communication in the brain, including direct soma-soma (**A1**) and synaptic contact (**A2**). **B–D** OPC somata ($PDGFR\alpha^+$, red) are in close contact with neuronal somata ($NeuN^+$, green) (arrows) in cortex (ctx, **B** and **C**) and hippocampus (hc, **D**). Micrographs in **B** and **C** are from the cortex of NG2-$CreER^{T2}$ × Rosa26-CAG-lsl-tdTomato mice [6, 133]. Images were acquired by confocal laser-scanning (LSM710, **B** and **C**) or automated epifluorescence microscopy (AxioScan.Z1) (**D**) with appropriate filters and objectives. Scale bars, 20 μm for **B** and 50 μm for **D**.

expression and even the functions of GABA receptors could differ between primary OPCs and stable cell lines. Indeed, a recent *in vitro* study showed that $GABA_B$ receptor activation favors primary OPC differentiation rather than self-renewal and survival [40]. Nevertheless, an *in vivo* investigation is necessary to clarify the exact biological function of GABA receptors. In fact, the conditional knockout of the $GABA_A$ receptor γ2 subunit during early development (p3–p5) does not influence OPC proliferation and differentiation [90]. Absence of the γ2 subunit reduces the number of OPCs without affecting differentiation into OLs, suggesting that γ2-mediated interneuron-to-OPC synapses might be required for the fine tuning of OPC self-maintenance [90].

Migration

OPCs maintain their density while migrating to either their target areas followed by differentiation or into sites of injury where they contribute to scar formation [9]. The migration is partially modulated by GABAergic signaling [95, 110], as has been shown for isolated primary OPCs and OPCs in explant preparations. Furthermore, this impact on migration appears to be more dominated by $GABA_A$ than $GABA_B$ receptor signaling, since it is blocked by the $GABA_A$ antagonist bicuculline, but not affected by $GABA_B$ antagonists [110]. However, $GABA_B$ receptors have been found to promote the migration of CG-4 cells [95]. Again, such differences might be due to the distinct properties of OPCs *in vivo* versus *in vitro* and changes in stable cell lines. Receptor expression as well as the ratio of $GABA_A$/$GABA_B$ receptors might change during the isolation and culturing processes. And most importantly, the microenvironment, i.e., the three-dimensional tissue organization including the stiffness and composition of the extracellular space, strongly influences migration. Therefore, *in vivo* studies are inevitably needed to address the impact of GABAergic signaling on OPC migration.

Monitoring Network Activity

OPCs receive GABAergic input in two non-exclusive modes, either directly *via* neuron-OPC synapses, i.e., contact sites between OPC processes and neuronal compartments including nodes of Ranvier, or, more diffusely, from GABA spillover from adjacent neuron-neuron synapses [20]. Close contacts between neuronal somata and OPCs have also been observed, although neurotransmitter-based connectivity is absent at such locations [111, 112] (Fig. 3A–D). About 40% of all cortical OPCs are in close contact with ~4% of all cortical neurons, and these are mostly GABAergic. These anatomically close pairs of neurons and OPCs do not communicate *via* synaptic structures. However, these cell-cell contacts could very well monitor neural network activity [113], similar to the way astrocytes sense their adjacent environment [114]. In the hippocampus, the pairs of OPCs and neurons can receive the same synaptic input from another neuron. OPCs closely apposed to neurons exhibit strongly synchronized excitatory postsynaptic currents [111]. Interestingly, in the cortex, such anatomical proximity is increased when mice are treated with the $GABA_B$ receptor agonist baclofen or the $GABA_A$ receptor antagonist picrotoxin. OPCs can sense presynaptic excitatory signals after positioning their soma and synapse close to interneurons and thereby regulate the local network. Considering the heterogeneity of OPCs [115], it is also possible that a certain subpopulation of OPCs favors this soma-soma communication. However, more *in vivo* experiments are necessary to address the cause and importance of such contacts.

Signaling Pathways of GABA Receptors in the OL Lineage

In OPCs, the activation of $GABA_A$ receptors induces membrane depolarization *via* Cl^- efflux. Concomitantly, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptor currents are inhibited [105]. The activation of $GABA_A$ receptors also raises the intracellular Ca^{2+} concentration [20, 84, 104, 116, 117] *via* at least two distinct pathways. (1) GABA-induced depolarization activates voltage-gated Na^+ channels expressed by OPCs. Subsequently, increases of intracellular Na^+ reverses the activity of the Na^+-Ca^{2+} exchanger and causes Ca^{2+} elevation in OPCs. This Ca^{2+} signaling pathway, without using VGCCs, is involved in the migration of OPCs [110]. (2) In the adult mouse cortex, GABA-evoked depolarization activates VGCCs, thereby directly elevating $[Ca^{2+}]_i$. and promoting the release of BDNF (brain derived neurotrophic factor) in the sensory-motor area and entorhinal cortex [104].

In contrast, the activation of $GABA_B$ receptors negatively regulates adenylyl cyclase *via* $G_{\alpha i/o}$ proteins and dampens the intracellular cAMP levels of OPCs [95]. Subsequently reduced protein kinase A activity suppresses gene transcription for BDNF and AMPA receptors *via* altered phosphorylation and the nuclear translocation of transcription factors such as CREB protein, thereby modulating synaptic and neural plasticity [118–120]. In cultured OPCs, $GABA_B$ receptor-mediated differentiation has also been shown to involve Src-family kinases, which are known to be associated with myelination [40]. Again, additional *in vivo* studies need to be carried out to elucidate

the exact downstream pathways of OL $GABA_B$ receptors ($G_{\alpha i/o}$ and/or G_q) and the potential involvement of cAMP and/or Ca^{2+} (Fig. 2B).

GABA Signaling Under Pathological Conditions

As the major inhibitory neurotransmitter in the brain, GABA plays crucial roles not only in physiological processes but also in many neurological disorders [121, 122]. To date, disturbances of GABAergic signaling have been robustly studied, but significantly less is known for the cells of the OL lineage.

In hypoxic regions associated with a stroke insult, GABA release is drastically increased at the penumbra [123, 124]. Counterintuitively, the $GABA_A$ receptor-mediated synaptic input to OPCs is reduced [22], but accompanied by extensive proliferation of OPCs, delayed OL maturation, and abnormal myelination [22]. This coincides with the finding that under physiological conditions GABA acts as neurotrophic factor. GABA *via* $GABA_A$ (at least γ2 subunit) receptors does not influence OPC proliferation and myelination [108], while $GABA_B$ receptor activation promotes myelination, at least *in vitro* [40], suggesting an inhibitory function of $GABA_A$ receptors in myelination. However, whether this communication is synaptic or extrasynaptic is unclear. Upon GABAergic stimulation, adult cortical OPCs produce neurotrophic factors like BDNF, which are increased after stroke [104]. BDNF, in turn, promotes OPC proliferation under physiological and pathological conditions [13, 14]. Whether the newly generated OPCs participate in the regeneration is unknown.

In a rat model of temporal lobe epilepsy, GABA-mediated inhibition is reduced due to two processes: (1) GABA synthesis is decreased mainly due to decreased GAD65 levels and (2) inhibitory postsynaptic currents (IPSCs) decline because of down-regulation of $GABA_A$ (especially subunits α1, γ, and δ) and $GABA_B$ receptors. However, $GABA_{A\text{-}\alpha5}$ and CREB are up-regulated [125]. As an effector of CREB, BDNF expression is increased by seizure activity, which in turn induces hyperexcitability in hippocampal neurons [126]. In mice with mutant CREB, epilepsy is suppressed, suggesting a potential therapeutic option to target epilepsy [127]. However, whether and how $GABA_A$ and $GABA_B$ receptor-CREB signaling pathways in OPCs and OLs also contribute to epileptogenesis needs further analysis.

Dysfunction of GABA-mediated OPC neurotransmission has not yet been demonstrated in multiple sclerosis (MS), a disease with progressive demyelination. But several reports suggest the importance of GABAergic signaling during the course of MS. In the brain of MS patients, both pre- and postsynaptic GABAergic neurotransmission are decreased [128, 129]. However, GABA level are increased in the sensorimotor cortex of MS patients but decreased in the hippocampus [130, 131]. With the knowledge that both $GABA_A$ and $GABA_B$ receptors are involved in OPC proliferation and differentiation under physiological conditions [18, 95], GABAergic neurotransmission of OPCs and OLs could also affect the disease progression of MS. Indeed, a recent single-cell RNAseq transcriptome study of mature OLs prepared from experimental autoimmune encephalomyelitis (EAE) mice revealed reduced levels of the $GABA_{B1}$ subunit, but unchanged levels of the $GABA_{B2}$ and $GABA_A$ receptor subunits [132]. As under physiological conditions, $GABA_B$ receptors of OLs also influence myelination in EAE. Interestingly, in these EAE mice, the expression of GABA transporter GAT3 is down-regulated in OPCs, while GAT1 is increased in OLs. However, the mRNA level of the transporter might not coincide with the respective transport activity. Therefore, elevations or reductions of extracellular GABA level cannot be inferred readily. In addition, under pathological conditions, GATs can reverse-transport GABA to the extracellular space. The scenario gets even more complex in light of the according timeline: Are expression changes of GATs a result of demyelination and thereby ahead of the remyelination failure or rather a consequence? Answering how GABAergic signaling in cells of the OL lineage is involved in de- and remyelination remains for the future.

Conclusion

GABA, a neurotransmitter as well as a neurotrophic factor, is synthetized and taken up by OPCs and OLs. For a long time, GABA has been recognized as the main mediator of neuronal inhibition. Now, we have learnt that this transmitter is broadly sensed by the OL linage, i.e., OL precursor cells as well as mature OLs. In contrast to neurons, however, in OPCs and OLs, GABA positively stimulates signaling cascades, mainly leading to enhanced Ca^{2+} levels. Thereby, GABA promotes myelination as well as neural recovery. GABAergic signaling in cells of the OL lineage cells represents an exciting novel field of research, especially the GABA-dependent interneuron-OPC communication. The concomitant analysis of OL differentiation and the modulation of neuronal network activity by distinct patterns of myelination will not only help to understand the normal brain but will be pivotal in complex neuropathologies that depend on temporally precise neuronal firing and transmission.

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