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Glutamate transporters: Expression and Function in Oligodendrocytes

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Abstract

Glutamate, the main excitatory neurotransmitter of the vertebrate central nervous system (CNS), is well known as a regulator of neuronal plasticity and neurodevelopment. Such glutamate function is thought to be mediated primarily by signaling through glutamate receptors. Thus, it requires a tight regulation of extracellular glutamate levels and a fine-tuned homeostasis that, when dysregulated, has been associated with a wide range of central pathologies including neuropsychiatric, neurodevelopmental, and neurodegenerative disorders. In the mammalian CNS, extracellular glutamate levels are controlled by a family of sodium-dependent glutamate transporters belonging to the solute carrier family 1 (SLC1) that are also referred to as excitatory amino acid transporters (EAATs). The presumed main function of EAATs has been best described in the context of synaptic transmission where EAATs expressed by astrocytes and neurons effectively regulate extracellular glutamate levels so that synapses can function independently. There is, however, increasing evidence that EAATs are expressed by cells other than astrocytes and neurons, and that they exhibit functions beyond glutamate clearance. In this review, we will focus on the expression and functions of EAATs in the myelinating cells of the CNS, oligodendrocytes. More specifically, we will discuss potential roles of oligodendrocyte-expressed EAATs in contributing to extracellular glutamate homeostasis, and in regulating oligodendrocyte maturation and CNS myelination by exerting signaling functions that have traditionally been associated with glutamate receptors. In addition, we will provide some examples for how dysregulation of oligodendrocyte-expressed EAATs may be involved in the pathophysiology of neurologic diseases.

Keywords

glutamate; glutamate transporter; oligodendrocyte; myelination; multiple sclerosis; neuropsychiatric disorders

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Compliance with Ethical Standards

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Introduction

Glutamate serves as the principle excitatory neurotransmitter in the central nervous system (CNS) of vertebrates and, as such, it has been implicated in a wide range of physiological processes, including neuronal differentiation, migration, survival, and neural plasticity [1–3]. Given its central role in neurotransmission, it is not surprising that dysregulation of glutamatergic mechanisms has been implicated in the etiology of diverse central pathologies including neuropsychiatric, neurodevelopmental, and neurodegenerative disorders [4, 5].

The above highlights the need for tight regulation of glutamate homeostasis in the CNS. Such regulation has been best characterized in the context of synaptic transmission at the socalled tripartite synapses [6], where pre-synaptically released glutamate is removed from the extracellular space by uptake through sodium-dependent glutamate transporters belonging to the solute carrier family 1 (SLC1), also termed excitatory amino acid transporters (EAATs) [7, 8]. Five glutamate transporters of the EAAT family have been characterized in the mammalian brain: GLAST (Glutamate/aspartate transporter, EAAT1, SLC1A3), GLT1 (Glutamate transporter 1, EAAT2, SLC1A2), EAAC1 (EAAT3, SLC1A1), EAAT4 (SLC1A6) and EAAT5 (SLC1A7) [9, 10]. Of note, the nomenclature for EAATs differs between species and has changed over time; for simplicity, the EAAT designations will be used throughout this review.

Members of the EAAT family share ~50% amino acid sequence identity along with structural and functional properties [11–13]. Nevertheless, EAAT family members display a number of subtle differences in characteristics such as glutamate binding affinity, transport rate, and regional and cell-type specific expression patterns [9, 13]. For many years it was believed that EAAT1 and EAAT2 are primarily localized to astrocytes of the gray matter to ensure glutamate clearance from the synaptic cleft [14, 15]. The distribution of EAAT3–5 was thought to be of non-glia origin with EAAT3 being expressed in neurons and non-neural tissues [16], EAAT4 in Purkinje cells of the cerebellum [17], and EAAT5 in photoreceptors and bipolar cells of the retina [18]. However, subsequent studies have revealed more refined expression patterns and alternatively spliced gene products with functionally diverse properties and/or distinctive expression profiles [9, 19, 20]. In addition, there is accumulating evidence for an expression of EAATs outside of the CNS [21]. In this context, the expression of EAATs has also been observed in myelinating glia of the CNS, namely oligodendrocytes. Currently, we are, however, only at the beginning of understanding the functional properties of EAATs in oligodendrocytes and their importance during CNS development and maintenance. In this review, we will provide a brief introduction into glutamate-mediated signaling as a potential regulator of CNS myelination followed by an overview of the current knowledge of EAAT expression in oligodendrocytes. In addition, we will discuss the known physiological functions of oligodendrocyte-expressed EAATs and their conceivable contributions to neurologic diseases.

Glutamate-mediated signaling in oligodendrocytes as a regulator of CNS myelination

As the most prevalent excitatory neurotransmitter in the vertebrate CNS, it is not surprising that glutamate has also been shown to affect cells of the oligodendrocyte lineage [22–25]. The progression of oligodendrocyte lineage cells through their maturation into myelinating cells can be simplified into three major stages: 1) oligodendrocyte progenitor cells (OPCs), which are proliferative and migratory, 2) pre-myelinating oligodendrocytes, which extend complex process networks in search of axonal segments to be myelinated, and 3) mature oligodendrocytes, which generate and maintain the myelin sheath [26, 27]. With regard to receptor-dependent glutamatergic signaling, it is noteworthy that OPCs have been well-described to form axo-glia synapses receiving input from electrically active axons via vesicular glutamate release [22, 25, 28, 29]. These synaptic contacts seem to occur predominantly on un- or de-myelinated axons, and they are thought to be unique to the progenitor stage of the oligodendrocyte lineage, disappearing once oligodendrocytes start to differentiate [29–32]. Functionally, synaptic axonOPC signaling has been proposed to contribute to the regulation of OPC migration, proliferation and differentiation; however, the emerging picture is complex and the specific role(s) of these synaptic contacts still remain(s) uncertain [25].

Further complicating is the finding that non-synaptic glutamate-mediated signaling may affect cells of the oligodendrocyte lineage at various stages throughout their differentiation. In this case, glutamate may be released by vesicular mechanisms and/or by the reversal of glutamate transporter activity [33]. Intriguingly, vesicular release at non-synaptic axo-glia junctions has been reported to promote the preferential myelination of electrically active axons in a well-established neuron-oligodendrocyte co-culture system [34]. This idea may be further corroborated by *in vivo* studies performed in the zebrafish in which electrically active axons were found to be preferentially myelinated and their myelin sheaths more likely to be preserved [35].

Overall, the ability of oligodendrocyte lineage cells to sense and respond to axonal electrical activity is thought to allow for activity-dependent fine-tuning of axon ensheathment, particularly during learning and memory consolidation [36–44]. Notably, such activityregulated myelination is considered to be part of a two phase – intrinsic/innate and adaptive – myelination process [45, 46] and to be a feature unique to axons of distinct sets of neuronal subtypes [47–50].

More recently, the concept of the axo-myelinic synapse has emerged, which proposes that receptor-dependent glutamatergic input from the axon is received at the myelin sheath along the length of an internode [43]; functionally, this junction has been implicated in coupling axonal electrical activity with metabolic output from the oligodendrocyte to preserve axon integrity and function [51, 52]. The above concepts highlight the two-way communication between the axon and the oligodendrocyte/myelin sheath that is likely mediated, at least in part, by receptor-dependent glutamatergic signaling.

In light of the increasing number of studies pointing toward critical roles of glutamatemediated signaling in oligodendrocyte biology and CNS myelination, it is unsurprising that oligodendrocytes have been described to express both ionotropic and metabotropic glutamate receptors throughout their lineage, the highest densities of which are found during the progenitor stages [30, 53, 54]. As reviewed in detail elsewhere, signaling through glutamate receptors has been implicated in regulating oligodendrocyte survival, proliferation, and differentiation, along with supporting long-term myelin maintenance and plasticity [22–25]. In addition to glutamate receptors, oligodendrocytes have been reported to express another family of glutamate-responsive transmembrane proteins recently shown to affect oligodendrocyte differentiation, namely EAATs [55]. In the context of glutamate-mediated signaling in oligodendrocytes, EAATs may thus play a so far under-appreciated role by not only contributing to the regulation of glutamate homeostasis but also glutamatergic signaling via a transporter-dependent pathway.

Expression of EAATs in oligodendrocytes

The advancements made in gene cloning approaches enabled the structural and molecular characterization of EAATs during the 1990s [16, 18, 56–58]; this, in turn, provided novel tools for analyzing the expression and function of EAATs and lead to the discovery of much broader and more complex EAAT expression profiles. In this context, first reports of an expression of EAATs in oligodendrocytes both in cultured cells and *in vivo* in the main white matter tract of the CNS, the corpus callosum, as well as the optic nerve were published in the mid- to late-1990s [59–63]. From these and subsequent studies, a summary of which is presented in Table 1, the following picture emerges:

With regard to EAAT3, there seems to be good consensus that it is expressed in cells of the oligodendrocyte lineage within the adult rodent brain, spinal cord, and optic nerve, although expression may be more prominent in immature oligodendrocytes and OPCs [59–62, 64–66]. In addition, oligodendrocyte EAAT3 expression has been reported for the optic nerve at postnatal ages 14–17 [67] and *in vitro* in cultures of differentiating oligodendrocytes [55, 63, 68, 69]. The idea that EAAT3 expression is downregulated as oligodendrocytes mature toward the myelinating stage is supported by gene expression data [70, 71]. On the other hand, no significant downregulation was found in cell culture studies [68], possibly indicating a less pronounced effect on EAAT3 expression under the *in vitro* conditions used in these studies.

Similar to EAAT3, most studies report an expression of EAAT1 in oligodendrocytes both in cultured cells as well as *in vivo* in the brain and optic nerve [55, 60, 61, 63, 66, 68, 69, 72, 73]. Nonetheless, under some experimental conditions the expression of EAAT1 in these areas appears to be undetectable in oligodendrocytes *in vivo* [67, 74, 75]. The latter observation is at present difficult to explain. However, several alternatively spliced variants have been described for EAAT1, one of which, namely GLAST1c, lacks exons 5 and 6 of the 10 GLAST mRNA encoding exons [76]. Interestingly, this variant was found to be strongly expressed by oligodendrocytes *in vitro* and *in vivo* [76]. Thus, it is conceivable that compared to an antibody recognizing an N-terminally located peptide sequence present in all known EAAT1 variants [60, 61], a cRNA *in situ* hybridization probe complementary to an

EAAT1 sequence including exons 5 and 6 [74, 75] may be less efficient in detecting GLAST1c expression due to the presence of non-complementary regions. It is of note, however, that the exact functions of GLAST1c are currently not fully understood and could include, next to bona fide transport activity, roles in regulating GLAST (full length) trafficking and/or yet unknown functional properties [76].

For EAAT2, DeSilva et al. [68, 77] described an *in vivo* oligodendrocyte expression pattern that is developmentally tightly regulated. In both human and rat white matter, EAAT2 expression was found to be largely restricted to the earlier stages of the oligodendrocyte lineage. In addition, EAAT2 mRNA expression levels in the corpus callosum were found to peak between 25 and 55 gestational weeks in human, a timeframe that precedes robust myelination [78]. Such developmental regulation is consistent with a lack of detection of EAAT2 expression in oligodendrocytes present in the adult CNS, as has been reported in a number of studies [60, 61, 73, 79, 80]. However, EAAT2 was seen on oligodendrocytes in the rat adult optic nerve when using immuno-electron microscopy [67] and detected by immunohistochemistry in the adult human brain and spinal cord [66, 69], suggesting persisting expression at low levels and/or species-specific expression pattern differences. As in the case of EAAT1, a number of alternatively spliced variants have been described, leading to differences in 5'-untranslated sequences, carboxy-terminal regions, and protein encoding exon sequences [19, 76, 81–83]. The expression of two variants with distinct carboxy-terminal regions, namely EAAT2a and EAAT2b, has been explored in oligodendrocytes. Both of these are expressed in differentiating oligodendrocytes in culture [68]. *In vivo*, EAAT1a was found to be expressed at the earlier stages of lineage development [68] but was not detected in oligodendrocytes in the adult CNS, according to most of the studies published to date [60, 61, 73, 74, 80]. Interestingly, EAAT2b has been reported to be present on oligodendrocytes in the adult CNS, at least in rodents and pigs [74, 80, 84]; it may thus represent the more prominent variant expressed in oligodendrocytes in the adult CNS. Functionally, it has been shown that EAAT2a and EAAT2b have similar transport characteristics [85]. However, the carboxy-terminal sequence of EAAT2b encodes a class 1 PDZ binding motif that is absent in EAAT2a, therefore suggesting interactions with intracellular scaffolding proteins unique to EAAT2b [82]. Currently, however, little is known about the proteins that interact with EAAT2b, and future studies will be necessary to dissect functional differences between EAAT2a and EAAT2b.

Taken together, the data published to date reveal an expression of EAAT1, EAAT2 and EAAT3 in cells of the oligodendrocyte lineage, whereas some controversies remain regarding the ability to detect EAAT1 in tissue sections. Overall, published findings support a developmentally regulated expression pattern of EAAT2, the highest expression of which is found in the earlier stages of oligodendrocyte development prior to robust myelination. In addition, there is evidence for a preferential expression of EAAT2b in oligodendrocytes in rodents, even though this expression may be somewhat species-specific. To our knowledge, oligodendrocyte expression of EAAT4 and EAAT5 has not been investigated in detail but based on gene expression data, EAAT4 appears to be expressed primarily in OPCs while there seems to be little to no expression of EAAT5 [71].

Oligodendrocyte expressed EAATs and their physiological functions

As alluded to in the introduction, the main function associated with EAATs is glutamate uptake via sodium-dependent glutamate transport. In this respect, it has been well-documented that EAATs are functionally active in oligodendrocytes. However, compared to astrocytes, significant kinetic differences have been reported with much lower Km and maximal velocity values measured in oligodendrocytes [61]. Assessing the uptake characteristics of oligodendrocytes along the progression from progenitor cell to pre-myelinating and then myelinating oligodendrocyte, DeSilva et al. [68] reported similar uptake characteristics for all maturation stages. Using pharmacological inhibitors with preference for EAAT1 or EAAT2, a primary contribution (78%−84.5%) of EAAT2 to glutamate uptake in oligodendrocyte was reported [60, 69]. A subsequent study, however, challenged this conclusion by arguing that at the concentrations used, the EAAT2 inhibitor also affected EAAT3 [68]. This latter study revealed EAAT3 as the major contributor (50%) to glutamate uptake into cortical rat oligodendrocytes with approximately equal contributions (~25%) by EAAT1 and EAAT2. Interestingly, electrophysiological recordings done in slice cultures showed higher contributions by EAAT2 in oligodendrocytes located in the spinal cord compared to those located in the corpus callosum [72]. Considering the source of oligodendrocytes used in the earlier studies, namely spinal cord [69] and forebrain [68], raises the possibility of regional differences in the contributions of the three transporters to glutamate uptake into oligodendrocytes. It is further noteworthy that glutamate transporter activity was found not to be restricted to the soma of the cell but also seen within oligodendrocyte processes [67]. Taken together, the above findings substantiate the idea that oligodendrocytes are capable of clearing glutamate from the extracellular space. This conclusion may be further supported by the observation that oligodendrocytes apparently possess all the machinery needed to metabolize glutamate [86–88].

In addition to glutamate clearance, there is increasing evidence for functional roles of EAATs beyond transport including the initiation of receptor-independent glutamatergic signaling cascades [89–92]. For example, transporter-dependent glutamatergic signaling has been found to suppress manganese-induced astrocyte stellation by a pathway that involves the stimulation of RhoA via tyrosine phosphorylation of RhoGEF followed by Rho kinase activation and inhibition of the actin depolymerizing factor cofilin as well as activation of the actin filament stabilizing factor myosin light chain, thereby leading to increased actin assembly and actin filament stability [89]. In addition, transporter-dependent glutamatergic signaling in Bergmann and retinal Müller glia cells has been described to regulate protein translation and transcription via the following signaling cascade: influx of sodium, as a consequence of transporter activation, is succeeded by an activation of the reverse mode of sodium-calcium exchanger activity leading to an increase in intracellular calcium levels; this initial signal is linked to protein translation via activation of mammalian target of rapamycin complex 1 (mTORC1) and to transcription via increased binding of activator protein-1 (AP-1) to DNA [91, 92]. Furthermore, our own data provide good evidence for a role of transporter-dependent glutamatergic signaling in promoting the morphological maturation of oligodendrocytes, which is characterized by extensive process outgrowth and branching [55]. In this case, activation of glutamate transport was also found to increase intracellular

calcium levels via activation of the reverse mode of sodium-calcium exchanger activity. In contrast to the observations made in Bergmann and retinal Müller glia cells, however, this calcium influx was not noticed to regulate gene expression but was found to promote the cytoskeletal remodeling necessary for process outgrowth and branching via, at least in part, phosphorylation of the actin binding site of calcium/calmodulin-dependent kinase II β [55]. The above examples highlight the complexity of transporter-dependent glutamatergic signaling, which may be regulated in a cell-type and/or context-dependent fashion. In addition, in light of our own findings and the emerging central role of axonal vesicular release of factors, including glutamate, in regulating adaptive myelination, it is tempting to speculate that glutamatedependent adaptive myelination may be mediated by signaling through not only glutamate receptors but also glutamate transporters.

Oligodendrocyte expressed EAATs and their potential contributions to neurologic diseases

Glutamate system disruption or dysregulation of glutamate homeostasis has been proposed to be a common contributor to a wide variety of neurologic diseases. As major regulators of glutamate homeostasis, EAATs have, not surprisingly, been proposed to be involved in the pathology of these diseases. In the following section, we present a few examples in which oligodendrocyteexpressed EAATs may be implicated in contributing to disease pathology.

Multiple Sclerosis (MS) is the major demyelinating disease in humans and represents the most common non-traumatic debilitating neurologic disease observed in young adults [93]. In MS, damage and/or loss of oligodendrocytes is thought to ultimately lead to chronic demyelination followed by degeneration of the underlying axon, thereby causing clinical symptoms and disability [94]. While immune-mediated myelin damage has traditionally been considered the primary pathologic feature of MS, there is increasing evidence that oligodendrocyte injury is a critical contributing factor [95]. However, the mechanisms involved in oligodendrocyte and axon injury are currently not fully understood. In this context, impairment of EAAT function has been proposed to play a key part in tissue injury in MS. Importantly, analysis of MS tissue revealed reduced levels of in particular EAAT2 expression in oligodendrocytes located in lesion adjacent normal-appearing white matter [66, 69]. This alteration has been interpreted to promote glutamate excitotoxicity, an idea that may be further supported by the observation that expression levels of the enzymes that mediate glutamate synthesis appear elevated in macrophages/microglia within early and chronic active MS lesions [66]. A correlation between the presence of activated microglia and loss of EAAT expression has also been reported by Vercellino et al. [96], even though oligodendrocyte expression was not assessed here. In light of the more recently reported role of EAATs in promoting oligodendrocyte maturation [55], a reduced expression of EAATs may not only promote injury but also compromise reestablishment of the myelin sheath under such pathologic conditions as seen in MS. Different from the above described observations of decreased EAAT levels, an increase in EAAT1 and EAAT2 expression in MS optic nerves has been reported for oligodendrocytes and astrocytes, respectively [73]. The exact reason for the apparent discrepancy is unknown; however, it is possible that disease mechanisms in MS may differ regionally. Alternatively, the patient samples used in the

different studies may represent different types of MS pathology in accordance with the now well-established concept of patient-dependent pathologic heterogeneity [97, 98].

Similar to MS, glutamate excitotoxicity has also been proposed to contribute to the pathology seen upon preterm birth in infants with very low birth weight, a condition that is associated with chronic neurologic disability in survivors. In this case, injury is thought to be due in large part to perinatal hypoxia leading to ischemic injury of vulnerable neurons and glia within the white matter, including cells at the earlier stages of the oligodendrocyte lineage that are often referred to as pre-oligodendrocytes [99, 100]. The exact reasons for this susceptibility to injury are not fully understood. Intriguingly, high levels of EAAT2 expression were found to coincide with vulnerability in pre-myelinating oligodendrocytes [68]. Thus, it has been proposed that the concurrent expression of glutamate receptors and glutamate transporters represents a significant component of vulnerability. More specifically, under the hypoxic conditions found in the preterm brain, EAATs, and in particular EAAT2, have been suggested to be functionally dysregulated to operate in a reverse mode that further increases extracellular glutamate concentrations; under these conditions excitotoxic cells death is promoted through glutamate receptor signaling. This idea may be supported by data demonstrating that the excitotoxic component of cell injury during oxygen-glucose deprivation or anoxia can be blocked by inhibiting EAATs [101, 102]. On the other hand, the extent of excitotoxic mechanisms involved in pre-oligodendrocyte injury in the developing brain is currently not fully understood [100]. In addition, despite pronounced loss of pre-oligodendrocytes during the acute phase, this event is followed by a significant increase in these cells, suggesting that loss of oligodendrocytes may not be the major cause of pathology later in life. Instead, dysregulation of pre-oligodendrocyte maturation may be the main culprit leading to neurologic disability upon preterm birth [103].

In addition to the above, alterations in EAAT expression and trafficking have been reported for a number of neuropsychiatric disorders including schizophrenia, which is also considered a neurodevelopmental disorder that is characterized by positive symptoms (i.e. delusions and hallucinations), negative symptoms (i.e. apathy), and abnormalities in cognitive functions [104, 105]. Interestingly, it has been suggested that medications managing negative and positive symptoms in schizophrenia may work, in part, by downregulating EAAT2 expression, thus suggesting that increased expression and function of EAAT2 may represent a mechanism by which glutamatergic signaling is dysfunctional in schizophrenic patients [106, 107]. However, lower levels of EAATs have also been reported [105, 108], and EAAT2 and EAAT1 genomic variants that are characterized by lower promoter activity and transporter expression have been associated with impaired cognitive and working memory performance in schizophrenia patients [109–111]. The above provides a glimpse of the complexity of EAAT-related changes in schizophrenia described so far, which may be represented by differential dysregulation in different brain regions and cell types as well as variability due to subject demographics, prior medication exposure and etiological as well as clinical heterogeneity [108, 112]. Nevertheless, there is overall good evidence that alterations in EAAT activity contribute to the pathophysiology of schizophrenia. More specifically, such alterations have been proposed to lead to excitotoxic neuronal loss and circuitry deficits as well as inefficient energy metabolism due to an impairment in glutamate recycling. However, there is also increasing evidence for

oligodendrocyte and myelin deficits in schizophrenia and their contribution to cognitive impairment [113–119]. In further support of the above, altered behaviors relevant to schizophrenia have been described for mouse models in which the expression of oligodendrocyte/myelin genes has been altered or oligodendrocyte loss and demyelination have been experimentally induced [119]. The emerging critical role of oligodendrocyte dysfunction together with the observation that EAAT-meditated signaling is involved in the regulation of oligodendrocyte maturation [55], raises the distinct possibility that EAAT alterations in oligodendrocytes may contribute to deficits in oligodendrocyte maturation and myelination and, thereby, play an important role in the pathophysiology of schizophrenia and the manifestation of cognitive dysfunction.

Conclusion

Sodium-dependent glutamate transporters, here referred to collectively as EAATs, have been well described to regulate extracellular glutamate homeostasis in the CNS via their expression and function in astrocytes and neurons. However, both the expression patterns and functional activities of EAATs are much more complex, with emerging roles in cells other than astrocytes and functional roles beyond extracellular glutamate clearance. In this context, we are currently only at the beginning of an understanding of the roles that EAATs may play in oligodendrocytes under both physiological and pathological conditions. Next to contributing to the regulation of extracellular glutamate levels, the findings to date suggest pivotal roles for oligodendrocyteexpressed EAAT1 and EAAT2 in adaptive myelination mediated by glutamate release from electrically active neurons. Further characterizing this role has the potential to not only reveal a better understanding of the developmental regulation of CNS myelination but also to provide further insight into the extent to which myelin abnormalities as seen under pathological conditions (p.e. Multiple Sclerosis and Schizophrenia) may be a consequence of dysregulated neuronal activity or dysregulated responses to neuronal activity in oligodendrocytes or both. Thus, gaining a better understanding of the mechanisms that trigger the activation of EAATs in oligodendrocytes and the downstream signaling pathways involved in regulating oligodendrocyte maturation and function is likely to result in the characterization of attractive novel therapeutic targets for treating neurologic diseases such as Multiples Sclerosis and Schizophrenia.

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Table 1.

Summary of data to the expression of EAATs in oligodendrocytes. EAAT2b (GLT-1b or GLT-1v), refers to one of the EAAT2 variants with a distinct carboxy-terminal region. OLG – oligodendrocyte, OPC – oligodendrocyte progenitor cell, P – postnatal day, N.D. – not detected.

EAATs expressed in oligodendrocytes	Experimental paradigm	Refer
EAAT1 EAAT2	RT-PCR analysis (for EAAT1, EAAT2) of oligodendrocyte cultures derived from rat brain (Wistar rat, newborn)	[63]
N.D. (EAAT1) N.D. (EAAT2)	non-radioactive *in situ* hybridization (for EAAT1, EAAT2) on sections from cerebellum, hippocampus, cortex and cervical spinal cord (male Wistar rats, 8–12 weeks old)	[75, 79]
EAAT3	radioactive *in situ* hybridization (for EAAT3) on brain sections (male Wistar rats, adult)	[62]
EAAT3	Immunohistochemistry (for EAAT3) on brain sections (Sprague Dawley rats, adult)	[59]
EAAT1 N.D. (EAAT2) EAAT3 (OPC)	immunohistochemistry (for EAAT1, EAAT2, EAAT3) on brain sections (bovine, adult)	[60]
EAAT1 EAAT2 EAAT3	RT-PCR analysis and immunocytochemistry (for EAAT1, EAAT2, EAAT3) of cultured cells derived from optic nerves (Sprague-Dawley rats, P12)	[61]
EAAT1 N.D. (EAAT2) EAAT3 (OPC)	immunohistochemistry (for EAAT1, EAAT2, EAAT3) on optic nerve sections (rat, adult)	[61]
EAAT3	non-radioactive *in situ* hybridization and immunohistochemistry (for EAAT3) on sections from brains and cervical spinal cord (Wistar rats, 8–12 weeks old)	[65]
EAAT3 (OPC)	immunohistochemistry on brain sections (male Wistar rats, adult)	[64]
N.D. (EAAT1; optic nerve) EAAT2 (only EAAT2b) EAAT3	non-radioactive *in situ* hybridization and immunohistochemistry on sections from brain, cervical spinal cord (EAAT2) and optic nerve (EAAT1, EAAT2, EAAT3) (male Wistar rats, adult)	[74, 80]
EAAT1 EAAT2 EAAT3	immunocytochemistry (for EAAT1, EAAT2, EAAT3) on brain and spinal cord sections (human, adult)	[66]
EAAT1 EAAT2	immunocytochemistry (for EAAT1, EAAT2) on oligodendrocyte cultures derived from spinal cord (human, 19–24 weeks of gestation)	[69]
EAAT1 EAAT2	non-radioactive *in situ* hybridization and immunohistochemistry (for EAAT1 and EAAT2) on sections from brain and spinal cord (human, adult)	[69]
EAAT1 N.D. (EAAT2)	immunohistochemistry (for EAAT1 and EAAT2) on sections from optic nerve (human, adult)	[73]
EAAT1 EAAT2 (whole cell recording)	immunohistochemistry and electrophysiological recordings (for EAAT1 and EAAT2) on sections from spinal cord and brains (bacterial artificial chromosome promoter reporter mice, PI–P40)	[72]
EAAT2 (pre-myelinating OLGs)	non-radioactive in situ hybridization and immunohistochemistry (for EAAT2) on sections from cerebral white matter (human, 19 weeks - 61 years)	[77]
N.D. (EAAT1) EAAT2 EAAT3	immunohistochemistry (for EAAT1, EAAT2, EAAT3) on sections from optic nerve (CNP-EGFP transgenic mice, P14–17)	[67]

EAATs expressed in oligodend rocytes	Experimental paradigm	Refer
EAAT1 EAAT2 EAAT3	immuno-electron microscopy (for EAAT1, EAAT2, EAAT3) on sections from optic nerve (rats, adult)	[67]
EAAT1 EAAT2 EAAT3	immunocytochemistry and Western blot analysis (for EAAT1, EAAT2, EAAT3) of oligodendrocyte cultures from rat brain (Long-Evans rats, newborn)	[68]
EAAT2 (OPC; pre-myelinati ng OLGs	immunohistochemistry (for EAAT 2) on brain sections (corpus callosum; Long-Evans rats, P1–P20)	[68]
EAAT1 EAAT2 EAAT3	Immunocytochemistry, qRT PCR and Western blot analysis (for EAAT1, EAAT2, EAAT3) of oligodendrocyte cultures derived from rat brain (Sprague-Dawley rats, P3)	[55]