

Why do oligodendrocyte lineage cells express glutamate receptors?

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Abstract

The function of glutamate receptors on oligodendrocytes and their precursor cells is poorly understood, with their only clear action being to damage these cells in pathological conditions. Here we review recent studies of glutamate signalling to oligodendrocyte lineage cells, and explore what its physiological function may be.

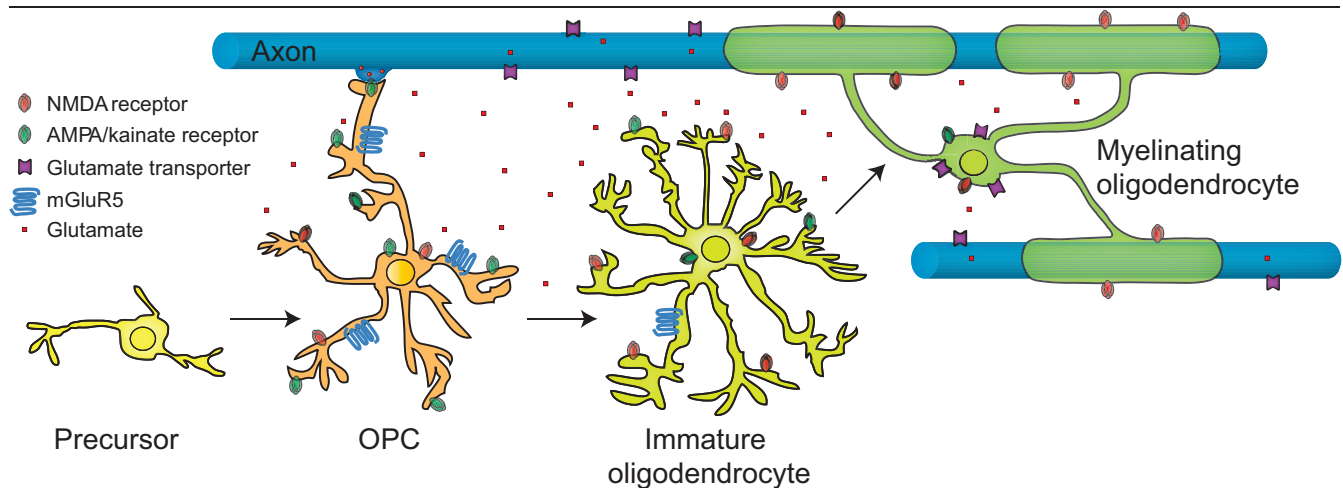
Introduction and context

Given the intimate association of neurons and glia in the central nervous system, it is not surprising that the main excitatory neurotransmitter, glutamate, is also recognized by a diverse group of resident glial cells. Oligodendrocyte lineage cells have long been known to respond to glutamate [1-3], but the only established effect of glutamate 'signalling' is the damage that these cells suffer in pathological conditions (for a review and relevant publications see [4]). For example, the extracellular glutamate level rises when glutamate transporters reverse in conditions such as stroke, or secondary ischaemia caused by blood vessel damage following spinal cord injury, or in development when inadequate blood flow reaches the white matter around the cerebral ventricles leading to cerebral palsy. Changes in the expression levels of the enzymes glutamate dehydrogenase, glutamine synthetase, and glutaminase also lead to a rise in extracellular glutamate concentration in multiple sclerosis lesions. An elevated glutamate level activates receptors that damage oligodendrocytes or, in the case of cerebral palsy, the precursor cells that will become oligodendrocytes. Are there, however, any positive aspects of glutamate signalling to oligodendrocyte lineage cells?

Major recent advances

A significant step forward came with the discovery that neurons send synaptic input to oligodendrocyte

precursor cells (OPCs) in the grey matter [5], and also in the white matter [6-8]. These contacts have the ultra-structural and pharmacological features of *bona fide* excitatory synapses involving glial α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate (KA) receptors (or GABA_A receptors: the intracellular [Cl⁻] is high in OPCs, so GABA is excitatory [9]). In the white matter this input was shown to occur from unmyelinated axons [7,8], prompting the notion that this could be a developmental signal from active axons, instructing nearby OPCs to stop proliferating and to start to myelinate the axons (Figure 1). Conceivably, such signalling could, with other known trophic factors, help to match the number of oligodendrocytes formed to the length of axon that needs to be myelinated. However, although previous work in culture showed that glutamate does inhibit the proliferation (and lineage progression) of OPCs [10], the demonstration that the synapses onto precursors are maintained through cell division [11,12] argues strongly against an immediate inhibitory effect of synaptic input on proliferation rate. Activation of AMPA receptors on OPCs might also promote OPC migration to sites of myelination [13], although it is not known whether glutamate released from neuronal synapses onto the OPCs can have this effect, and migration would seem to be incompatible with maintaining the presence of synapses from particular axons. AMPA/KA receptors on OPCs might also trigger

Figure 1. Glutamate receptor expression on oligodendrocyte lineage cells

Schematic depiction of a myelinating oligodendrocyte (right) that has differentiated from a mitotic progenitor (oligodendrocyte precursor cell [OPC], left), which was in synaptic contact with an unmyelinated axon. OPCs, immature oligodendrocytes, and mature oligodendrocytes express glutamate receptors. Axonal and oligodendrocyte glutamate transporters cause a non-vesicular glutamate release in conditions of energy deprivation such as stroke and secondary ischaemia following spinal cord injury. Whether glutamatergic stimulation of OPCs regulates their differentiation and myelination awaits *in vivo* evidence. AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, NMDA, *N*-methyl *D*-aspartate; mGluR, metabotropic glutamate receptor.

metabolic interactions between axons and ensheathing glia [14]. As OPCs mature into myelinating oligodendrocytes, the synaptic input from axons is lost [15,16] (Figure 1).

Amplification of the effect of excitatory synaptic input onto OPCs was recently suggested to occur because a subpopulation of OPCs (identified by their expression of the oligodendrocyte specific transcription factor Olig2 and the proteoglycan NG2) express voltage-gated Na^+ channels that, at least in some rat OPCs, are present at a density sufficient to evoke action potentials [17]. In contrast, another subclass of OPCs neither received synaptic input nor fired action potentials [17]. Studies on mouse OPCs (identified by expression of dsRed driven by the NG2 promoter) reported no action potentials in Na^+ -channel-expressing OPCs [15], and it was suggested that the action-potential-generating cells were migrating interneurons rather than OPCs. However, this is hard to reconcile with their expression of Olig2 and NG2 and their lack of expression of NeuN [17]. Indeed, recent work on mouse OPCs (labelled with green fluorescent protein expressed under control of the *Pdgfra* or *Sox10* promoters) revealed that the size of the voltage-gated Na^+ current in these cells was fivefold smaller than in rat OPCs [18], resulting in spike-like regenerative activity being much weaker [12,18,19]. Excitatory synaptic input will tend to activate the voltage-gated Na^+ current, and thus depolarize the cell further, while simultaneously raising $[\text{Na}^+]_i$. These effects will promote

a rise of $[\text{Ca}^{2+}]_i$ [20], but whether this alters the migratory behaviour of OPCs, regulates differentiation, or leads OPCs to release some factor onto other cells currently remains obscure.

It is of increasing interest to define the receptor subtypes mediating glutamatergic signalling to oligodendrocyte lineage cells, and their subcellular location. It was originally believed that ischaemic damage to oligodendrocytes and their precursors resulted solely from the activation of AMPA/KA receptors, but increasing evidence implicates NMDA (*N*-methyl *D*-aspartate) receptors as well. Applying glutamate or NMDA activates NMDA receptor- as well as AMPA/KA receptor-mediated currents in the cells [6,15,17,21]. In ischaemia, activation of NMDA receptors is partly responsible for damage to developing OPCs [21] and to the myelinating processes of oligodendrocytes [22,23], and (along with KA receptor activation) contributes to retraction of the paranodal folds from the node of Ranvier [24], raising the question of whether glutamate receptors are preferentially localized at the paranodal folds of the myelin. However, the extent to which blocking NMDA receptors preserves the function of myelinated axons after ischaemia requires further investigation [25,26]. The NMDA receptors involved show less Mg^{2+} -block than neuronal NMDA receptors [6], suggesting that they have an unusual subunit composition [6,22,23]. Surprisingly, given these results, transcriptome analysis [27] indicates that although NMDA receptors are expressed in OPCs, their expression at the mRNA level

drops to low levels as the cells mature into myelinating oligodendrocytes, yet immunocytochemistry suggests that NMDA receptors are present both on the myelinating processes of oligodendrocytes [6,22,23] and on developing oligodendrocyte precursors [21]. A similar down-regulation of AMPA receptors with development has also been reported [15,16].

NMDA receptors do not seem to contribute to synaptic currents evoked in OPCs by neuronal activity [7,8,15,16], raising the question of what their physiological function may be. One suggestion, based on experiments in which dorsal root ganglion cells are myelinated by OPCs in culture, is that the growth factor neuregulin produces a switch in the mode of myelination by OPCs: without neuregulin added to the culture medium myelination is independent of neuronal activity and glutamate release, while with neuregulin added myelination depends both on action potentials and on activation of NMDA receptors [28]. Myelination is generally thought to depend on action potentials [29], but myelination of fixed axons (which clearly have no action potentials) has also been reported [30] and this may correspond to the activity-independent mode of myelination seen in these studies.

In addition to ionotropic glutamate receptors, developing oligodendrocytes in culture and *in vivo* express metabotropic glutamate receptors (mGluRs), particularly mGluR5, which is downregulated as the cells mature [27,31-33]. The function of these receptors is unclear but, in cultured OPCs, activation of group 1 mGluRs (presumably mGluR5) raises $[Ca^{2+}]_i$ [31], leads to the release of brain-derived neurotrophic factor [34] (which could promote myelin formation), and reduces both excitotoxic damage to the cells and apoptosis induced by staurosporine [32,33,35].

Future directions

Considerable work will be required to establish the true function of glutamatergic signalling to oligodendrocyte lineage cells. Genetic engineering in mice will provide some insight into the roles of particular glutamate receptor subtypes. However, for a phenomenon as important as myelination, it is likely that several mechanisms will operate in parallel, and with functional redundancy in place mutant phenotypes may not be informative. There are several crucial aspects of neuron-to-glia signalling that we need to establish. Is it only the glutamate that is released at synapses onto OPCs that is functionally relevant, or can tonic activation of high-affinity NMDA receptors also modulate cell function? What is the role of glutamate transporters, which are

reported either to generate a large current in mature oligodendrocytes [15,16] or to greatly reduce the glutamate-evoked current [6]? What are the pathways downstream of glutamate receptors that control OPC development and myelination, and does this signalling contribute to determining whether OPCs develop into oligodendrocytes, or into astrocytes or neurons [36-38]? Do these pathways also function to maintain myelination in the adult animal? Are there functions of glutamatergic signalling other than regulation of oligodendrocyte development? Does glutamate signalling play a role in the formation of the glial scar in pathology, or in remyelination, since adult OPCs receive glutamatergic synaptic input as they migrate during remyelination [39]?

Abbreviations

AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; KA, kainate; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl *D*-aspartate; OPC, oligodendrocyte precursor cell.

Competing interests

The authors declare that they have no competing interests.

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