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Trends Cell Biol. Author manuscript; available in PMC 2014 December 01.

Published in final edited form as:
Trends Cell Biol. 2013 December ; 23(12): . doi:10.1016/j.tcb.2013.07.007.

Oligodendroglia metabolically support axons and maintain structural integrity

Brett M. Morrison, **Youngjin Lee**, and **Jeffrey D. Rothstein**
Brain Science Institute, Dept of Neurology, Johns Hopkins University

Abstract

Axons are specialized extensions of neurons that are critical for the organization of the nervous system. In order to maintain function in axons that often extend some distance from the cell body, specialized mechanisms of energy delivery are likely necessary. Over the last decade, greater understanding of human demyelinating diseases and the development of animal models have suggested that oligodendroglia are critical for maintaining the function of axons. In this review, we will discuss evidence for the vulnerability of neurons to energy deprivation, the importance of oligodendrocytes for axon function and survival, and very recent data suggesting that transfer of energy metabolites from oligodendroglia to axons through monocarboxylate transporter 1 may be critical for the survival of axons. This pathway has important implications both for the basic biology of the nervous system as well as for human neurologic disease. New insights into the role of oligodendroglial biology provide an exciting opportunity for revisions in nervous system biology, understanding myelin-based disorders and in therapeutics development.

Keywords

MCT1; oligodendroglia; neurodegeneration; myelin; ALS; lactate

Unique Vulnerability of Neurons

Neurons are specialized cells in the nervous system capable of integrating thousands of inputs (i.e., synaptic afferents) into a single output (i.e., action potential). In long projection neurons, such as corticospinal tract neurons, spinal motor neurons, and dorsal column sensory neurons, action potentials are transmitted by the axon (Glossary) several feet before terminating on another neuron or end organ, such as muscle. Some axons are so extensive that up to 99% of the neuron's cytoplasm is contained within the axon. This unique anatomy of a neuron is the critical component of the emerging field of connectome analysis (i.e., how functional connections between different areas of the central nervous system (CNS) lead to specific behaviors)[1], but may also be a source of unique vulnerability to the neuron. Many of the proteins necessary for axon function, including structural proteins, ion channels, molecular motors, and synaptic vesicle proteins, are translated in the soma and transported into, and in some cases to the end of, axons. Constant metabolic energy is necessary for axonal transport, as well as to maintain the sodium gradient (through Na+/K+ ATPases)

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Brain Science Institute, Johns Hopkins University, 855 N. Wolfe St., Rangos 270, Baltimore, MD 21205 USA., jrothstein@jhmi.edu, Tel: 410-614-3846.

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necessary for action potentials. Together, these features make axons "energetically expensive" to maintain [2].

Energy for the axon, in the form of ATP, is partly generated from glucose transporters on neuronal cell bodies, but it is likely that local energy is required to maintain axon function along its long course. Access to extracellular glucose is restricted in most long axons by the presence of myelin (Glossary), a hydrophobic barrier surrounding axons. Myelin, which is formed by oligodendroglia (Glossary) in the CNS and Schwann cells in the peripheral nervous system (PNS), is critical for efficient impulse conduction in the axon. Instead of having to activate channels throughout the axon, the sodium and potassium channels can be focused in discrete regions that lack myelin, termed nodes of Ranvier or juxtaparanodes, respectively (Glossary) [3]. Since up to 99% of the axons' surface area is covered in myelin, only a small percentage of the axon is actually exposed to the extracellular space, limiting access to glucose and other energetic metabolites in the extracellular space. For this reason, it has been postulated that axons derive some metabolic energy directly from oligodendroglia through their myelin sheaths [4].

Evidence for a local supply of energy to axons came initially from studies of optic nerve explants. *Ex vivo* preparations of optic nerve propagate compound action potentials (CAPs) for several hours after dissection, and thus allow sensitive physiologic readout of nerve function in various media conditions [5]. In the absence of glucose, optic nerve explants maintained CAPs for approximately 30 minutes and irreversible nerve injury can ensue after 60 minutes. Pretreatment of the nerves with high glucose to induce production of glycogen in resident astrocytes extended the latency for an additional 15 minutes until CAP failure and prevented much of the permanent nerve injury. CAP failure could also be prevented by lactate administration, which was predictably blocked by lactate transport inhibitors [6, 7]. These experiments suggested that astrocytes support neurons by exporting lactate produced from glycogen through monocarboxylate transporters (MCTs). As will be detailed below, recent evidence suggests that oligodendroglia are the prominent site of lactate export to neurons, though astrocytes may play a critical role in sustaining energy substrates through their glycogen stores and production of lactate through glycolysis.

Oligodendroglia are critical for axon function/survival

Oligodendroglia are specialized cells in the CNS that wrap axons with myelin. Diseases of oligodendroglia invariably produce some degree of demyelination (Glossary), which was thought to underlie their clinical signs and symptoms (Text Box 1). Over the last 10 years, animal studies have demonstrated a critical role for oligodendroglia in the maintenance and long-term survival of axons and neurons and may yield clues to the involvement of oligodendrocytes in neurodegenerative diseases. Multiple transgenic models of oligodendrocyte injury have been investigated, including several with perturbations of proteolipid protein (PLP; Glossary), 2’,3’-cyclic-nucleotide 3’-phosphodiesterase (CNP; Glossary) knockout mice, and diptheria toxin conditional transgenic mice (Table 1). These animal models produce varying degrees of demyelination and progress over different time frames, but all of the models consistently demonstrate axonal pathology. These genes and models of axonal pathology will be discussed below.

PLP is the most abundant protein present in myelin. Though its exact function remains unclear, it appears to be important for shuttling some myelin proteins, such as septins and sirtuin 2 [13], from the soma into the myelin sheaths. Several different PLP animal models have been investigated, including naturally occurring point mutations [14– 18], PLP1 overexpression rats [19] and mice [20, 21], and PLP1 knock-out mice [22, 23]. It is outside the scope of this review to discuss these in any detail, but many of these animal models

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demonstrate axon degeneration associated with (e.g., PLP1 point mutations and overexpressor rodents) or without (e.g., PLP1 null mice) demyelination; and in some cases axon degeneration has been directly linked to decreased axonal transport [21, 22]. The exact mechanism for axon degeneration in these mice is unknown, though it may involve abnormal intracellular trafficking of mRNA or protein, for example, metabolic transporters necessary for axonal integrity, since a number of myelin proteins are reduced or absent in these animal models.

A second oligodendroglia gene that can lead to axonal injury is CNP. CNP is an RNA binding protein that may function to promote intracellular RNA transport by binding RNA to tubulin [24]. CNP null mice develop CNS pathology reflecting degeneration of either axons or oligodendroglia including spheroids (Glossary) and myelin ovoids, likely from failure of axonal transport and disruption of structural components of the paranode (Glossary), and later develop muscle atrophy, weight loss, hydrocephalus, and premature death [25][26, 27]. Interestingly, these mice do not have demyelination at ages when the axon degeneration is prominent. The etiology of axon degeneration is unclear but given the disrupted paranodal architecture, it likely involves failure of oligodendrocytes to interact with axons. Though the pathology of CNP null mice is similar to PLP1 disrupted mice, the mechanism of degeneration must be different since double knockout mice develop increased axonal degeneration compared to either null mouse alone [27]. Thus, the disruption of oligodendroglial proteins with different cellular functions such as PLP1 and CNP can lead to a common phenotype of severe disruption of axon function and integrity.

Recent studies have also investigated the impact of acute death of oligodendroglia on neuron function and survival. Oligodendroglia cell death was induced by crossing a conditionally targeting diphtheria toxin to PLP-CreER mice [28] or by treating mice with diphtheria toxin in which the oligodendroglia have been sensitized by selectively expressing diphtheria toxin receptor within them [29, 30]. In these models, the diptheria toxin led to rapid and selective oligodendroglial death via the blockade of protein synthesis. Though the clinical severity differed between the mice, one model developed a rapid spastic paralysis and died within 3 weeks [30], another developed motor deficits, tremor, ataxia without early death [28], and the third model developed tremor and gait abnormalities only [29], all models of oligodendroglia death produced severe axonal injury characterized by accumulation of non-phosphorylated neurofilaments and amyloid precursor proteins [30]. Though some of these mice exhibited abnormalities in myelin composition, overall myelination was not affected, suggesting that axonal injury is not due to demyelination [30]. Additionally, axon injury is not dependent on the secondary immune reaction since it persisted after crossing to an immunodeficient line of mice [28]. These studies demonstrate that oligodendroglia themselves, and not just components of myelin, are critical for maintaining axons.

Taken together, these animal models strongly suggest that perturbation of oligodendroglia cause axon injury, at least partly through disruption of axon transport, as reflected by the altered morphology and axonal inclusions (e.g. spheroids, multivesicular bodies) which are dependent upon normal axonal transport. The exact mechanism by which this occurs is not known, but another recurring theme from the animal models is that oligodendroglia intracellular trafficking often appears to be disrupted. Perhaps oligodendroglia support of axonal transport is dependent on one or more molecules in the myelin sheath and failed trafficking to the myelin sheath leads to axonal pathology. Though there are several possible myelin proteins that may play a role in supporting axons, recent data suggests that transporters for monocarboxylates are critical for maintaining axon integrity. Failure of these transporters to be expressed in oligodendroglia would reduce the availability of local metabolic energy to the axon [31][32], potentially impacting energy-dependent processes in the axon such as axonal transport [4, 33].

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MCT1 is critical transporter for axon support by lactate

MCTs are extracellular membrane channels that transport lactate, pyruvate and ketone bodies, along with protons, down their concentration gradient across membranes (see [34] for review). Based on sequence homology, 14 members have been identified, though only MCT1, 2, and 4 localize to the CNS and co-transport monocarboxylates and protons. Transport can be enhanced by decreasing pH or increasing substrate concentration, as would be expected for passive diffusion [35]. In the CNS, MCT1 is expressed predominately in oligodendroglia and a few specific neuronal populations [32, 36], though it may be present in much smaller amounts in astrocytes and endothelial cells [37, 38]. MCT2 is expressed primarily in neurons [39–41], and MCT4 in astrocytes [40, 41]. The cellular distribution and physiologic properties of MCTs led to the lactate shuttle hypothesis [42]. In this hypothesized mechanism for energy transfer between cells, a heavily glycolytic (i.e. non-oxidative) cell produces large amounts of pyruvate that is converted to lactate and transported extracellularly down its concentration gradient through specific MCTs. The extracellular lactate is then transported into cells dependent on oxidative metabolism by other MCTs, converted to pyruvate and then used by the Kreb's cycle to produce ATP. This cellular interdependence is hypothesized to occur between astrocytes and neuron (i.e., astrocyte-neuron lactate shuttle)[43]. Recently published work has modified this hypothesis by showing that oligodendroglia are critical intermediaries for lactate transport to neurons [31, 32].

Downregulation of MCT1, which is present almost exclusively within oligodendroglia in the CNS, resulted in axon injury and/or neuron cell loss *in vitro* and *in vivo* (Figure 1)[32]. Treatment of spinal cord organotypic cultures with anti-sense oligonucleotides or a specific pharmacologic inhibitor to MCT1 (MCT1i) led to motor neuron cell loss, though they required prolonged treatment. Motor neuron, as well as other neuron, loss was accelerated by incubating the sections in glucose-free media. Glucose deprivation makes neurons completely dependent on lactate as a source of metabolic energy and neuron loss following treatment with MCT1i was immediate. Importantly, loss or blockade of MCT1 was not toxic to oligodendroglia *in vitro*, and neuron death was prevented by adding exogenous lactate. These *in vitro* experiments support the hypothesis that failed lactate release from oligodendroglia, not blockage of uptake and oligodendroglia energy failure, was responsible for neuron loss. These *in vitro* experiments provided the mechanistic support for several experiments *in vivo* demonstrating the neurotoxicity of MCT1 attenuation.

In each of the *in vivo* experiments (Figure 1), MCT1 expression was attenuated either globally (*i.e.*, MCT1 heterozygous null mice or lentiviral constructs expressing shRNA driven by non-specific promoters) or selectively within oligodendroglia (i.e., cellspecific promoters or Cre-expressing transgenic mice) [32]. In all of these studies, downregulation of MCT1 resulted in axon degeneration. Furthermore, when injected focally into the spinal cord, MCT1 shRNA caused not only axon degeneration but also motor neuron loss. Together, these experiments confirmed the findings observed *in vitro* that downregulation of MCT1 produces axonal degeneration and, in some cases, neuron loss.

Given its known role as a transporter of lactate and its localization in the myelin sheaths surrounding axons [44], these studies suggested, for the first time, that oligodendroglia MCT1 is a key transporter of energy metabolites to axons, and that attenuation of MCT1 produces axon pathology due to local energy failure within the axon. A limitation to these studies, however, is that lactate flux is never measured directly, rather it is inferred by indirect measurements of axonal injury, and loss of MCT1 could potentially cause axon degeneration through other mechanisms. Further support for a role of lactate came from transgenic experiments in which oligodendroglial mitochondria were selectively targeted by

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mutations in cytochrome oxidase [31]. In the CNS, no pathology was seen even at 9 months of age, likely due to stable mitochondria produced prior to conditional expression of cytochrome oxidase mutations, but brain lactate measured by MR spectroscopy was increased in mice under isofluorane anesthesia. Alterations in brain lactate likely result from increased export of lactate from oligodendroglia forced to utilize non-oxidative metabolism due to mitochondrial mutations. Interestingly, the levels of lactate rapidly returned to that of control after discontinuing anesthesia, possibly due to rapid uptake by neurons/axons. Though this study makes several assumptions about metabolic activity in anesthetized neurons and oligodendroglia (i.e., reduced metabolic activity in neurons but not in oligodendroglia), it provides further support for a direct role of oligodendroglia in the supply of lactate to axons.

In aggregate these recent studies provide strong evidence for a new role of oligodendroglia in direct energy substrate support of axons (Figure 2). However, there are several issues raised by these studies that need to be further addressed, including the role of astrocytes in energy supply to neurons, whether MCT1 on oligodendroglia is an exporter or importer of lactate, and whether lactate is truly the critical energetic molecule for direct energy supply to axons.

Astrocytes: Possible link between oligodendroglia and nutrient supply

Although these aforementioned studies provide strong evidence for the role of oligodendroglia in directly supplying energy support to axons, alternative cells including astrocytes could also be directly or indirectly involved in supplying energy to neurons. There is substantial literature on astrocytes supplying lactate to neurons (see [45, 46] for recent reviews). Much of the early literature is based on isolated cultures and therefore may not be reflective of *in vivo* physiology, since these transporters are known to change expression in culture conditions [32]; however several recent studies have investigated the role of lactate and astrocytes *in vivo*. These experiments, including studies in ischemia [47], lactate utilization by functional imaging studies [48], and memory function [49, 50], demonstrate that lactate is critical for neuronal energy supply *in vivo* and that neurodegeneration or neuronal dysfunction results from interfering with this pathway. In both studies on memory function, an important role for the astrocyte was indirectly implicated due to dependence on glycogen utilization, which is almost exclusively present within astrocytes in the CNS [51]. None of these studies *in vivo* prove, however, that the supply of lactate to neurons is directly from astrocytes, since none of the modifications were astrocyte-specific. By combining results obtained from both astrocyte and oligodendroglia studies, it is possible that astrocytes transfer energy metabolites directly to oligodendroglia, which in turn supports neurons/axons.

Oligodendroglia make direct connections with astrocytes in the form of gap junctions (Figure 3). These gap junctions are composed of 2 oligodendroglia proteins, connexin 32 (Cx32) and 47 (Cx47), that form heteromeric channels with astrocyte connexin 30 (Cx30) and 43 (Cx43), respectively [52]. These connexins appear to be important for oligodendroglia (and likely Schwann cells) function since mutations of Cx32 produces CMT1X, an inherited peripheral neuropathy [53], and Cx47 produces Pelizaeus-Merzbacher-like disease (PMLD), a severe childhood onset leukodystrophy characterized by nystagmus, ataxia and spasticity [54]. Transgenic mice null for both Cx32 and Cx47 develop profound CNS demyelination, axonal injury, tremors, seizures, and premature death by 2 months of age [55]. In addition, Cx47 and Cx30 double null mice, which effectively disconnect gap junctions between oligodendroglia and astrocytes, also develop myelin pathology, motor impairments, and die by 3 months of age [56]. Although the function of astrocyte-oligodendrocyte gap junctions is not well clarified, they are capable of

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transporting energy metabolites such as glucose [57] and presumably could also transport lactate. Though speculative at this point, transport of lactate from highly glycolytic astrocytes to oligodendroglia through gap junctions could provide some of the energy substrates shuttled into the periaxonal space by oligodendroglial MCT1. If demonstrated experimentally, this hypothesized metabolic connection between astrocytes, oligodendroglia, and axons would explain prior studies showing the critical nature of both astrocytes and oligodendroglia in the support of axons. Ultimately, these findings may help to support the astrocyte neuron lactate shuttle model by extending it to include oligodendroglia as critical intermediaries for at least some of the lactate supply to neurons.

Directionality of lactate transport

The directionality of lactate transport through MCT1 in oligodendrocytes is critical for understanding their function. As importers of lactate, oligodendrocytes likely use lactate for their own energetic needs. If indeed they export lactate, they are likely supporting the metabolic needs of other cells. Determining the direction of transport in vivo is quite difficult to evaluate experimentally. MCTs are bi-directional transporters with the direction of transport being determined by the relative intracellular and extracellular concentration of substrates (*i.e.*, lactate and hydrogen ions). Thus far, lactate transport has only been measured *in vitro*, where directionality is determined by the components of the media. Though excellent *in vitro* tools for measuring lactate transport are available, there is no sensitive tool for measuring lactate transport *in vivo*. Despite this, several lines of indirect evidence support the conclusion that oligodendroglia are generally exporters, not importers, of lactate [32]. First, it was found that exogenous lactate completely prevented neuron loss in organotypic cultures produced by blocking oligodendroglia MCT1 transporters, presumably by substituting for the lactate unable to be released from oligodendroglia due to the MCT1 inhibitor[32]. Second, oligodendroglia death was not seen *in vitro* or *in vivo* after attenuation of MCT1[32]. Third, MCT1 is predominantly localized to the myelin sheath around CNS axons as would be expected for an exporter of lactate to axons, and not to the cell body[32]. Fourth, as described above, selective mitochondrial deficits in oligodendroglia that enhance lactate production within oligodendroglia lead to increased extracellular lactate when neuronal function is suppressed by an anesthetic [31]. Of course, lactate may also be imported into oligodendroglia, either through MCT1 or another mechanism, and contribute to the production of myelin, as has been shown in dissociated [58] and cortical slice cultures [36], but attenuation of MCT1 does not appear to cause neuron or axon degeneration through this mechanism.

Alternative oligodendroglia-based energy Sources

The final issue raised by these studies is whether the energy metabolite transported by oligodendroglia MCT1 is lactate. Most of the discussion of alternative energy sources to glucose centers around lactate, but MCTs can also transport pyruvate and ketone bodies such as β-hydroxybutyrate and acetone. In fact, ketone bodies and pyruvate can also be produced by astrocytes, and thus contribute to the supply of energy to neurons (see [59] for review). Ketone bodies are produced by astrocytes from fatty acids, particularly when glucose supply is limited, and they can readily be used for energy by neurons. Ketone body production is dependent on supply of fatty acids, not glycogen, and therefore it is not responsible for glycogen-dependent memory function, as detailed previously [49, 50]. Pyruvate could also function as an alternative source of energy to neurons. It is produced in the brain by astrocytes, and unlike ketone bodies, is a product of glycogenolysis. It can be rapidly utilized by neurons as an energy source *in vitro*, though a role *in vivo* has not yet been shown. The disadvantage of pyruvate is not to neurons, but rather to the producing astrocyte. In order to perpetuate glycolysis, NAD^+ must be regenerated. In the setting of oxidative metabolism, this is accomplished by mitochondria; however, in non-oxidative

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metabolism, NADH is oxidized to NAD+ as pyruvate is metabolized to lactate. Despite this, it is possible that astrocytes oxidize NADH by an alternative pathway and pyruvate may to some extent be an important energetic molecule to neurons. In summary, astrocytes are capable of producing a number of energy intermediaries that can be transported through MCTs and each may be used under different metabolic conditions. Blocking MCT1 reduces transport of all of these intermediaries and therefore does not delineate which one (or ones) is critical for support of axons.

Potential implications for disease

In addition to being critical for understanding basic cell biology, the recent discovery that oligodendroglia supply energy directly to axons through MCTs also has possible ramifications for human disease. Deficits in axonal energy, such as mitochondrial failure, have been implicated in Alzheimer's disease, Parkinson's disease, Huntington's disease, hereditary spastic paraplegia, and amyotrophic lateral sclerosis (ALS). All of these adult-onset neurodegenerative diseases demonstrate "dying back" neuropathy suggesting early failure of axon function. In most of these diseases (or more specifically, in cellular or animal models for these diseases), axon transport has been directly shown to be deficient, and in others, axon pathology was prominent, indirectly implicating failure of axon transport (see [60] for review). Though deficits in axon transport do not necessarily result from energy failure and could be due to damage to molecular motors, tubulin scaffolding or other factors, it is intriguing that energy failure may play a role in this diverse group of diseases. Though general defects in axon transport or early pathology to axons indirectly implicates energy pathways in axons, there is more direct evidence for this role in ALS.

ALS is a progressive neurodegenerative disease characterized pathologically by the loss of both upper and lower motor neurons. Despite the importance of motor neuron loss to the development of symptoms, recent work has suggested that glia, including astrocytes, microglia and very recently oligodendroglia [61–63], contribute to the death of motor neurons. In two very recent publications, oligodendroglia were found to degenerate in mutant SOD1 transgenic mice, a mouse model of ALS, and though replaced by differentiation of oligodendroglia precursor cells (OPCs), appear to be dysfunctional [62, 63]. Though the full scope of this dysfunction is not known, oligodendroglia in the ventral spinal cord of SOD1 transgenic mice and motor cortex from patients with ALS were both deficient in MCT1 [32]. Additionally, removing the toxic mutation in SOD1 from OPCs, and subsequently from newly generated oligodendroglia, resulted in marked attenuation of disease progression[63]. Given the deleterious effects of reducing oligodendroglia MCT1 on motor neurons [32], these results suggest that reduced expression of MCT1 in oligodendroglia is one mechanism contributing to motor neuron degeneration in ALS. Further work evaluating mechanisms to protect oligodendroglia or increase MCT1 transport activity in models of ALS should shed further light on the importance of oligodendroglial MCT1 in ALS.

Concluding Remarks

Oligodendroglia have increasingly been recognized as important contributors to axon function and survival. Several human diseases of oligodendroglia produce axon injury, as do a number of mouse models, but until recently, the mechanism by which oligodendroglia support axons was unknown. Recently published studies have shown that oligodendroglia express MCTs and disruption of these transporters leads to axon injury and neuronal death, suggesting that supply of energy metabolites to axons, in the form of lactate (or possibly ketone bodies and pyruvate), is a critical function of oligodendroglia *in vivo*. Further work is necessary to determine whether oligodendroglia support axons through other mechanisms as

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well as the importance of these transporters in diseases affecting oligodendroglia (see Outstanding Questions).

Glossary

2',3'-Cyclic-nucleotide 3'-phosphodiesterase (CNPase)	Protein component of myelin with unclear cellular role, though may be important for intracellular transport
Axon	Specialized component of neuron that electrochemically interconnects brain regions through action potential propagation
Demyelination	Reduced quantity of myelin covering axons, can be either diffuse or focal
Oligodendroglia	Non-neuronal cells in the central nervous system that myelinate and support axons
Juxtaparanode	Region adjacent to paranode in which the potassium channels cluster in the axon
Myelin	Multi-laminar covering of axons composed of both lipid and protein components
Node of Ranvier	Intermittent gaps in myelin at which voltage-dependent sodium channels cluster in axon
Paranode	Region adjacent to node of Ranvier in which the myelin sheaths contact the axon
Proteolipid protein (PLP)	Most abundant protein component of myelin in the CNS
Spheroid	Focal pathologic axon swelling composed of disorganized neurofilaments, microtubules and transported organelles.

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TEXT BOX1. Oligodendroglial Dysfunction in Human Disease

The diseases most directly associated with oligodendroglia injury are multiple sclerosis (MS) and inherited leukodystrophies. MS is an autoimmune disease most commonly characterized by relapsing-remitting neurologic symptoms and signs. Patients frequently have multiple "neurologic events" characterized by subacute, progressive development of weakness, numbness or vision loss that frequently improves (i.e., remits) to some degree. These events reflect new focal areas of demyelination in the CNS that reduce the efficiency of action potentials. Over time, the myelin is repaired and the symptoms remit. Importantly, however, most patients eventually reach a progressive stage of the disease in which the symptoms do not remit and autopsies of MS patients show not only demyelination but also significant axon injury and neuron loss [8]. A second group of oligodendroglial diseases are inherited leukodystrophies, including Pelizaeus-Merzbacher disease (PMD) produced by mutations in the proteolipid protein 1 gene (PLP1), Pelizaeus-Merzbacher-like disease produced by mutations in Connexin 47 (Cx47), and adrenoleukodystrophy due to mutations in a peroxisomal enzyme necessary for degrading very long chain fatty acids. In addition to oligodendroglial injury and demyelination, these diseases also produce varying degrees of axon injury that ultimately lead to the most disabling neurologic symptoms [9–12].

These human diseases suggest a role for oligodendroglia in supporting axons; however, all of these diseases also cause demyelination and most produce secondary inflammation. Due to this, it is unknown whether the axon injury is a direct result of oligodendrocyte injury or secondary to downstream events. For this reason, transgenic mice have been studied in which the impact of oligodendrocyte injury can be separated from demyelination and inflammation.

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Outstanding questions

- How do oligodendroglia obtain sufficient glucose and/or lactate for transport to axons?
- Does a connexin-based network of oligodendria and astroglia underlie this metabolic support?
- Is the MCT1 transporter in oligodendroglia (and other metabolic transporters) and MCT2 transporter in axons concentrated to certain regions of the myelin sheath and axolemma (e.g. paranodal regions) where energy demands in the axon might be greatest?
- Are there ways to enhance MCT-based transport in oligodendroglia or axons that could be protective and thereby therapeutic?

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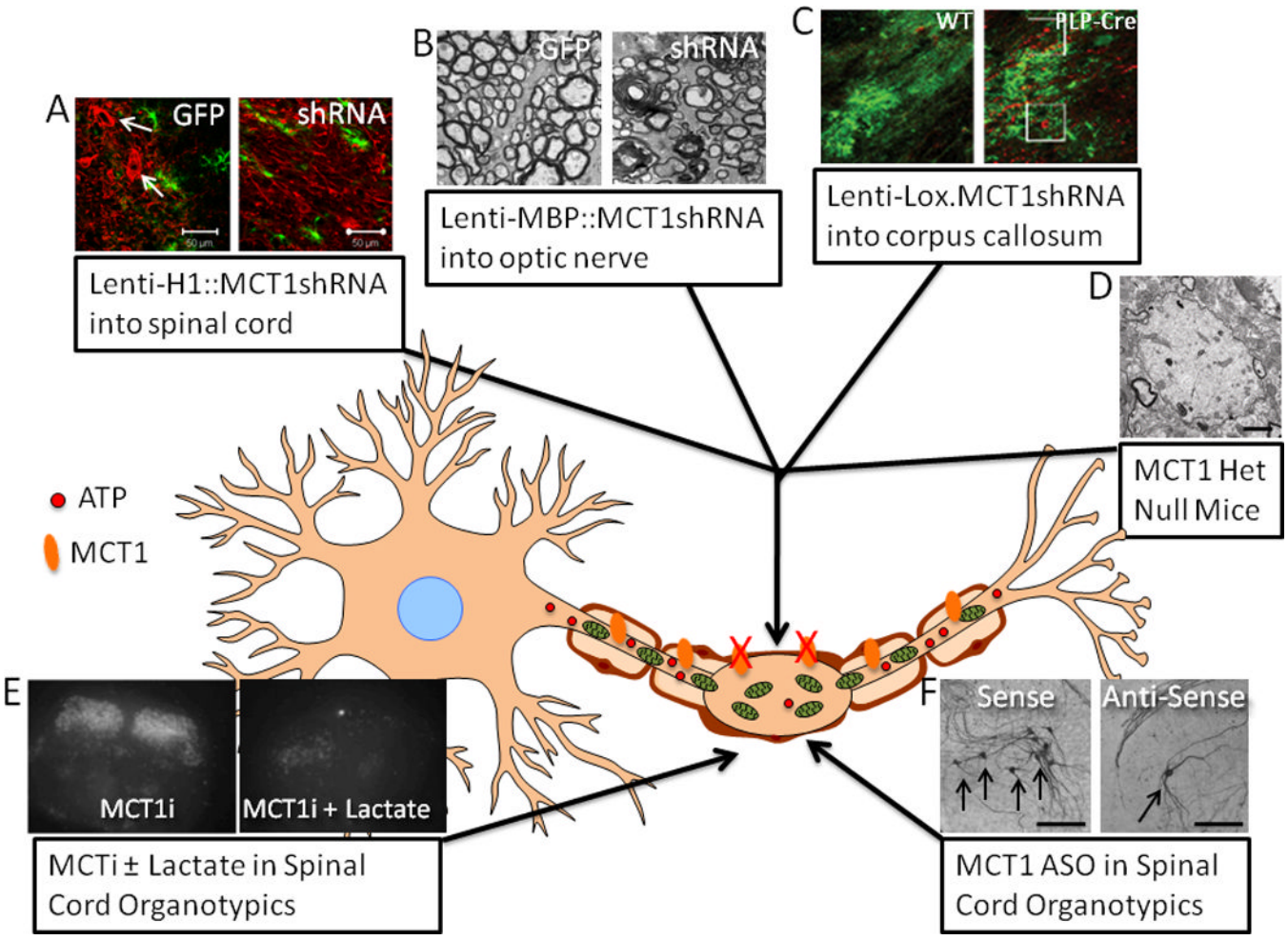

Figure 1.

Multiple manipulations that attenuate MCT1 in rodent models (A–D) or spinal cord organotypic cultures (E,F) produce motor neuron cell death (A,F; arrows indicate motor neurons), spinal neuron cell death (E; propidium iodide) or axon injury (B–D).

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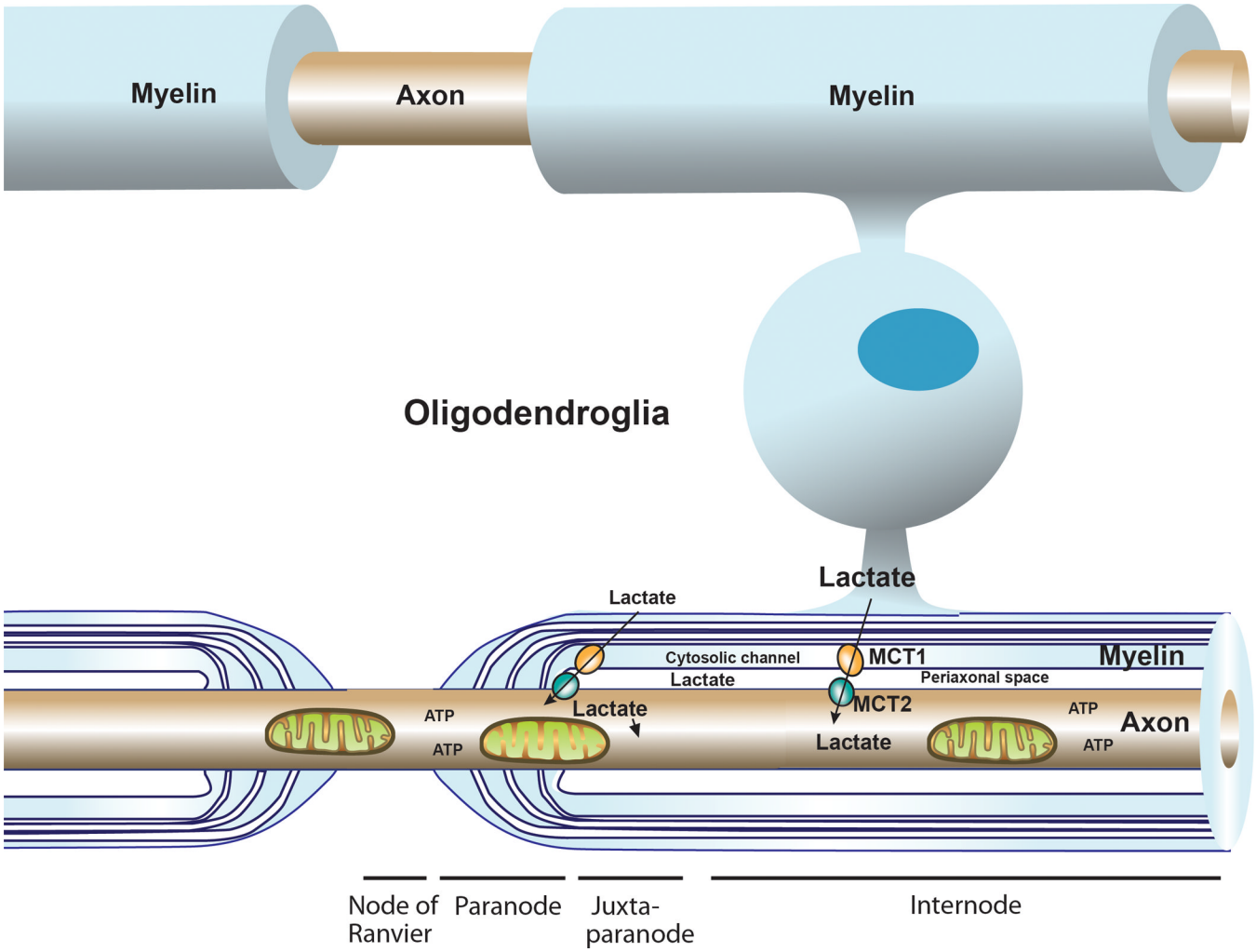

Figure 2.

Schematic of oligodendroglia and axonal monocarboxylate transporters. Oligodendroglia transport lactate, or other monocarboxylates, to the periaxonal space through MCT1. From this space, lactate can be taken up into axons by MCT2, converted to pyruvate by lactate dehydrogenase, and imported into mitochondria for oxidative phosphorylation and the subsequent generation of ATP.

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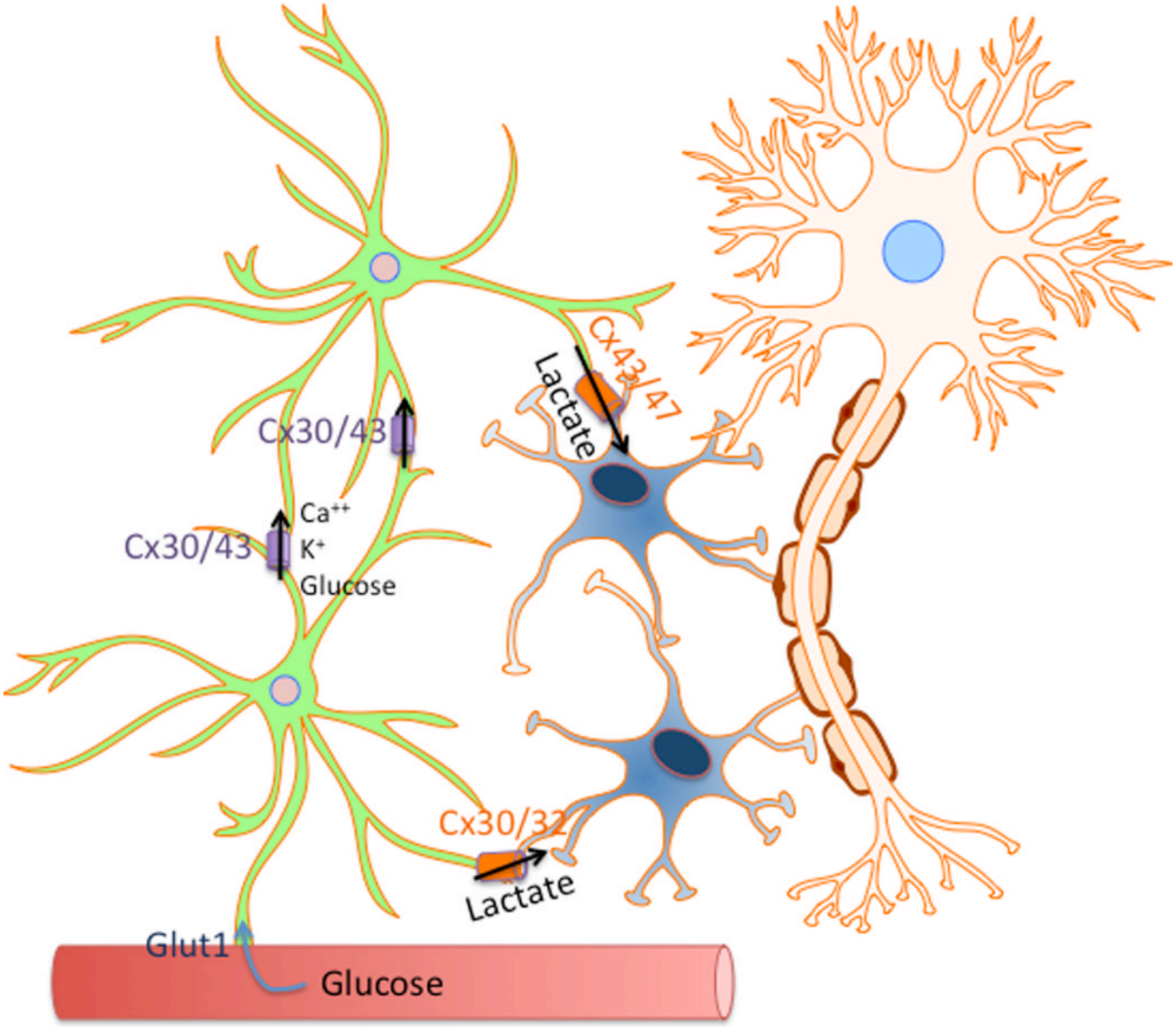

Figure 3.

Astrocytes and oligodendroglia form a syncitium connected together by gap junctions formed by specific connexin molecules. Though just a hypothesis, lactate may transport from astrocytes to oligodendroglia through gap junctions prior to being used as axonal energy.

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Table 1

Pathology and mechanism of axon injury in multiple rodent models and human diseases involving oligodendrocytes. Definitions; 2',3'-cyclic-nucleotide 3'-phosphodiesterase (CNPase), proteolipid protein 1 (PLP1), Connexin 47 (Cx47), diphtheria toxin (dT).

Rodent Model or Human Disease	Mechanism	Oligodendroglia/ Myelin Pathology	Axon Pathology	Refs
PLP1 Mutant Mice (Jimpy/ Rumpshaker)	PLP1 point mutations	Demyelination Variable oligodendroglia injury	Mild (Jimpy)	16,17,18
PLP1 Null Mice	PLP1 null	Normal	Spheroids Slow transport	22,23
PLP1 Overexpressor Mice	PLP1 over	Demyelination	Spheroids Slow transport	21
CNPase Null	CNPase null	Grossly normal Subtle ultra-structural deficits	Spheroids Severe and early.	25,26,27
dT Mice	Oligodendrogliad eath	Oligodendroglia loss Variable Demyelination	Spheroids, Abnormal Nodes	28,29,30
Pelizaeus-Merzbacher Disease	PLP1 duplications/mutations	Oligodendroglia loss Demyelination	Spheroids	9,10,11
Pelizaeus-Merzbacher-Like Disease	Cx47 mutations	Demyelination	Spheroids	12