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Oligodendrocyte-derived transcellular signaling regulates axonal energy metabolism

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Abstract

The unique morphology and functionality of central nervous system (CNS) neurons necessitate specialized mechanisms to maintain energy metabolism throughout long axons and extensive terminals. Oligodendrocytes (OLs) enwrap CNS axons with myelin sheaths in a multilamellar fashion. Apart from their well-established function in action potential propagation, OLs also provide intercellular metabolic support to axons by transferring energy metabolites and delivering exosomes consisting of proteins, lipids, and RNAs. OL-derived metabolic support is crucial for the maintenance of axonal integrity; its dysfunction has emerged as an important player in neurological disorders that are associated with axonal energy deficits and degeneration. In this review, we discuss recent advances in how these transcellular signaling pathways maintain axonal energy metabolism in health and neurological disorders.

Keywords

ATP supply; axonal energetics; energy metabolism; exosome; glycolysis; metabolite shuttling; mitochondria; myelin; oligodendrocyte; neurodegeneration

INTRODUCTION

The mammalian CNS is a well-integrated network comprised of two main cell classes: neurons and glial cells; the latter subclassified as astrocytes, microglia, and OLs. These glial cells provide physical and metabolic support to neurons, modulate neuronal communication, and maintain microenvironment homeostasis [1]. In the CNS, OLs enwrap lipid-rich myelin sheaths in concentric spirals around axons with diameters larger than 0.2 μm [2].

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Nodes of Ranvier, which are periodic gaps between myelin segments that are exposed to the extracellular space, accelerate the conduction of nerve impulses [3,4]. The bulk of myelinated axons localizes within the white matter, which is organized into tracts for fast transmission of information to connect different brain regions into functional circuits [5]. While myelin sheaths cover most of the axonal surface for electrical insulation, it also limits the rapid access of metabolites and nutrients from the extracellular environment to the axonal cytoplasm. Because of their unique association with CNS axons, OLs are well-positioned to act as metabolic intermediaries between myelinated axons and the extracellular matrix. Generic studies of OL-specific proteins provide early evidence that OLs support axonal integrity and survival beyond acting as passive electrical insulators. For example, knockout (KO) mouse models of proteolipid protein 1 (PLP1) or 2'–3'-Cyclic nucleotide 3'-phosphodiesterase (CNP) exhibit severe axonal degeneration in the absence of alterations in the electrical conduction properties of the axon [6,7]. The myelin basic protein (MBP)-null "shiverer" mice maintain intact axons despite demyelination [8,9]. The deficits in information processing upon demyelination in MBP-deficient mice were similar to those resulting from a reduction in axoglial metabolic support [10]. These studies highlight important roles for OLs in supporting axonal integrity independent of electrical insulation.

The brain is one of the most energy-demanding organs in the body: it consumes nearly 20% of the body's total cellular energy in the form of adenosine triphosphate (ATP) [11]. Glucose is the predominant source of carbon for the generation of ATP under physiological conditions, whereas alternative energy substrates (such as lactate, acetate, and ketone bodies) are also supplied to neurons for generating ATP when glucose supply is limited [12–15]. Glucose metabolism generates ~95% of the ATP in the brain jointly through glycolysis and oxidative phosphorylation (OXPHOS). Each glucose is catabolized by glycolysis into two ATP molecules and two pyruvate molecules which are subsequently transferred into the mitochondrion for entry into the tricarboxylic acid cycle, producing 30–36 ATP molecules through OXPHOS [16]. The complete oxidation of glucose gives a near stoichiometric ratio of oxygen to glucose consumption of 6:1, which is the most efficient metabolic pathway in neurons to fulfill their energy demand (Figure 1).

Axonal terminals utilize approximately 55% of the total ATP in neurons, where most energy is used to maintain resting potentials, fire action potentials, and sustain synaptic vesicle (SV) recycling [17–20]. An energy budget estimates that optic nerve axons with diameters smaller than 0.9 μm have a 38% deficit in ATP production compared to their ATP consumption [21]; these axons likely require energetic support from neighboring cells. This provides a theoretical basis for OLs to support axonal energy metabolism, thus opening an emerging theme relevant to a range of neurological disorders, as axonal mitochondrial dysfunction and energetic failure have been observed in human OL-deficient diseases and animal models for hereditary spastic paraplegia (HSP), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) [22–25]. In this short review, we limit our discussion to current knowledge and new insights into the transcellular OL-neuron signaling in support of axonal energy metabolism through metabolite shuttling and exosome signaling. We also summarize emerging lines of evidence showing how deficient OLs impair axonal energy metabolism in neurological disorders. For additional insights from different perspectives of OL-derived

support in neuronal metabolism and function, we refer readers to other in-depth reviews [26–31].

Neuronal adaptation to energetic stress

Neurons adopt special mechanisms maintaining local ATP supply through coordinating glycolysis and OXPHOS in distal axons and synapses, where bioenergetic failure is particularly vulnerable and relevant to neurodegenerative diseases [32]. Revealing these mechanisms is an emerging frontier for therapeutic investigation. For instance, intensive synaptic activity places a large burden on the axonal energy budget. Neurons rapidly respond to activity-induced energetic stress by activating the AMP-activated protein kinase (AMPK) energy-sensing pathway, which recruits glucose transporter type 4 (GLUT4) to presynaptic membranes to enhance glucose uptake and glycolytic activity [33,34]. To maximize ATP production capacity, activity-dependent activation of AMPK further recruits axonal mitochondria to presynaptic terminals via myosin VI and mitochondrial anchoring protein syntaphilin (SNPH) [18], and/or remodels mitochondrial cristae ultrastructure to support the energy-expensive SV recycling under long-term synaptic activation [35]. In the CNS, acute axonal injury causes severe damage to the cellular environment and mitochondrial bioenergetics. In mature neurons, axonal mitochondria largely remain stationary, and those damaged mitochondria at injury sites cannot be replaced by healthy ones, leading to local energy crisis [32,36]. The insufficient ATP supply in injured axons is among one of the key intrinsic factors leading to regenerative failure [37,38]. Thus, turning off SNPH-anchoring through an energy-signaling cascade in injured axons allows healthy mitochondria to be delivered into injured areas, thereby facilitating axonal regeneration by rescuing the energy crisis [39]. Although glycolysis is an important aspect of axonal maintenance and growth cone dynamics [40], it remains elusive whether glycolytic activity alone is sufficient to maintain axonal energy metabolism after CNS injury. By trafficking healthy mitochondria to the injury sites, neurons can partially restore axonal energy supply to power regeneration, which requires high levels of energy. Considering the intricate networks in the human brain where billions of neurons and glial cells wire together, this raises an urgent question of whether additional energetic support from neighboring glial cells is beneficial for neurons to maintain axonal energy homeostasis under energetic stress. With myelin sheaths covering up to 98% of the CNS axonal surface, OLs are well-positioned to provide metabolic support to maintain axonal integrity [26,27].

Transcellular OL-neuron metabolic signaling

The energetic metabolic strategies employed in OLs—A single OL can myelinate up to 50 axons, wrapping as many as 150 layers of myelin membrane around each axon [28]. This large cellular expansion places enormous energetic demands on OLs. Analytical calculations predict that ~6.84×10^{21} ATP molecules are needed to produce 1 gram of myelin protein and 48-fold that per gram of myelin lipid [21]. To meet this energetic demand, OLs employ a metabolic strategy heavily relying on mitochondria before and during myelination, with a high density of long, tubular mitochondria to support high OXPHOS rates [41]. Upon completion of myelination, the number and size of mitochondria in the mouse OL processes are dramatically reduced, with only half the density and length of neuronal mitochondria [42–44]. Consistently, a metabolic profiling study using stable

isotope tracing revealed a higher glycolytic than oxidative metabolic activity in the white matter of rat brains [45], suggesting a metabolic shift towards glycolysis in mature OLs. This metabolic switch in OLs is in the opposite direction as neuronal differentiation: a switch from glycolysis to mitochondrial OXPHOS occurs during differentiation of human neural stem cells to mature neurons [46]. Therefore, OLs and neurons exhibit large diversity in transcriptomic, proteomic, and metabolomic landscapes [47–49]; OLs serve as an ideal metabolic supplement for axonal energy production by providing metabolites and proteins that are in short supply in neurons generally through two pathways: (1) shuttling energy substrates, such as glucose, lactate, and pyruvate, that can be directly metabolized by neurons for energy production and (2) secreting exosomes containing proteins, RNAs, and other materials that boost neuronal energy metabolism.

Metabolite shuttling—OLs serve as metabolite reservoirs for neurons by uptaking glucose as their main carbon source from blood circulation through glucose transporters type 1 (GLUT1) [50]. Under high levels of glucose, the rate of glycolytic pyruvate production in the cytosol exceeds its rate of mitochondrial utilization, thus excess pyruvate is converted to lactate, the end-product of anaerobic glycolysis. The reversible conversion of lactate to pyruvate is catalyzed by lactate dehydrogenase (LDH). Evidence for OL-axon metabolic signaling initially came from studies of mouse optic nerve explants where axons are completely myelinated [23,51]. As intracellular lactate accumulates, it can pass from the OL soma through myelinic channels to reach the inner tongue processes enwrapping an axon. Lactate is released into the periaxonal space through the monocarboxylate transporter 1 (MCT1), and subsequently taken up by axons via the neuronal isoform MCT2, presumably fueling neuronal mitochondrial OXPHOS [23] (Figure 2). It is worth noting that pyruvate is passively transported to axons through the same mechanism as lactate through MCTs [51]. The lactate/pyruvate exchange between OLs and neurons are determined by axonal energetic demands. Overproduction of lactate could result in lactic acidosis, which causes irreversible cell damage and is detrimental for both grey and white matter functions [52]. Therefore, the glucose utilization and the glycolytic rate in OLs is tightly adapted to meet different axonal energy demands and to avoid excessive lactate production.

N-methyl-D-aspartate receptors (NMDARs) are expressed in the myelinating processes of OLs and activated by neuronal glutamate release, thus relaying neuronal energy demand to nearby OLs. The activation of NMDARs mobilizes GLUT1 to myelin sheaths, resulting in increased glucose uptake and glycolytic activity leading to lactate build-up in OLs [50]. This OL-derived lactate shuttling through MCT1 provides on-demand metabolic support to axonal compartments. The role of MCT1 in maintaining axonal integrity has been elucidated in animal models, where heterozygous MCT1-null mice develop widespread axonopathy with no change in overall myelination by 8 months of age [23]; mice with deletion of MCT1 develop late-onset hypomyelination and significant axonal degeneration [53]; blockade of glial MCT function in *Drosophila* cause age-dependent neuron loss [54]. While these studies highlight MCT1 in the maintenance of axonal integrity independent of myelination, the effect of MCT1 deletion on axonal ATP availability or axonal lactate content has not been directly addressed. Although it is well established that OLs deliver lactate to axons and neurons employ lactate as an energy substrate [55–59], the evidence that neurons can

metabolize OL-derived lactate is still indirect. An *ex vivo* imaging study in transgenic mice expressing a FRET-based ATP sensor revealed that electrical activity firing in acutely isolated optic nerves reduces axonal ATP content, suggesting that axonal glycolysis products are not sufficient to maintain activity-enhanced mitochondrial energy metabolism on their own [60]. This study strongly argues for a critical role of oligodendrocytes in delivering energy substances to axons of CNS neurons.

The brain also adapts its metabolism by switching from glucose-based to lipid-based fuel sources under low glucose availability [15,61]. Lipids are key molecules of the brain's structure and function and comprise ~50% of the brain's dry weight [62]. It is estimated that up to 20% of total brain energy required for the maintenance of basal activity is provided by fatty acids [63]. While neurons do not store a significant pool of lipid droplets, astrocytes and OLs are the main cell types reserving lipid components in the brain. Astrocytes metabolize fatty acids through mitochondrial β-oxidation and export ketone bodies such as acetoacetate and β-hydroxybutyrate through MCTs, which can be taken up and utilized by neighboring neurons for energy production [64]. In the *Drosophila* starved brain, the cortex astrocyte-like glia fuel neurons with ketone bodies as an energy substrate to support memory function [15], suggesting an alternative metabolite shuttling pathway between glia and neurons. As myelination is largely dependent on continuous lipid synthesis [65], OLs are suppliers of lipid metabolites, which have been proposed to serve as energy reserves when circulating glucose is low [66]. During normal myelin turnover, myelin lipids are recycled by the autophagy-lysosomal pathway, thus liberating fatty acids for synthesis of new myelin lipids. When glucose availability is reduced, OLs break down myelin, allowing free fatty acids to undergo β-oxidation to create acetyl coenzyme A (acetyl-CoA), an entry substrate for mitochondrial OXPHOS. By utilizing ATP generated through myelin catabolism, OLs are capable of sharing more glucose-derived pyruvate/lactate with the axonal compartments in a mouse optic nerve model system [66]. Such a shift from normal myelin turnover to lipid-based ATP generation is essential for OL survival, as well as transiently reversing axonal energy deficits under low glucose conditions. Based on assumptions about metabolite shuttling coupled with lipid catabolism, this study provided new insights into how OLs adapt to nutrient stress to protect axons from hypoglycemia-induced degeneration. The metabolic switch from glucose-based to lipid-based fuel serves as a systematic chronic adaptation during the progression of aging-related neurodegenerative disease, including Alzheimer's Disease (AD). Glucose hypometabolism and a compensatory shift to ketone body-based energy production has been reported as a metabolic phenotype of the AD brain in both clinical and preclinical studies [67,68]. Mitochondrial function is compromised in the early stages of AD [69]. Declined mitochondrial respiration in the mouse brain leads to the catabolism of myelin sheaths by activating phospholipase-A_2 sphingomyelinase, thus myelin catabolism provides ketone bodies to fuel an energetically-compromised brain during glucose hypometabolism [70]. However, the extended breakdown and catabolism of myelin lipids is detrimental to myelin integrity, resulting in white matter demyelination and axonal degeneration, which is a common pathological hallmark of AD.

Metabolite shuttling also engages panglial networks to coordinate glial metabolite provisions to meet the energetic demands of the brain [71]. Both astrocytes and OLs uptake glucose from blood circulation through GLUT1 and supply lactate/pyruvate to neurons through

MCTs [29,72]. Intriguingly, brain glucose is stored as glycogen almost exclusively in astrocytes, where glycogen is broken down to glucose, which is metabolized by glycolysis to produce pyruvate and lactate [73,74]. Astrocyte-derived glucose and lactate/pyruvate is transported to OLs through gradient-dependent diffusion along GLUTs, MCTs, and connexin channels during glucose deprivation [75,76]. One can speculate that OLs further deliver the glucose and lactate/pyruvate to myelin-covered axons, which astrocytes have limited access to. Although the flow direction and mechanisms regulating metabolite transfer from astrocytes to neurons through OLs remain largely unclear, these studies suggest a role for panglial networks in metabolite provisions to axons (Figure 2).

Extracellular vesicle (EV) signaling—EV signaling is increasingly recognized for intercellular communication. EVs are heterogenous membranous structures released by cells into the extracellular space, allowing exchange of proteins, lipids, and RNA molecules. EVs can be subclassified as exosomes which are produced through the endocytic pathway with a diameter of 30–100 nm, and ectosomes which are shed from the plasma membrane with a diameter of 50–1000 nm [77]. Exosomes are secreted via exocytosis into the extracellular space and taken up by the recipient cell. In the CNS, both glia and neurons release exosomes under physiological and pathological conditions, and these exosomes play critical roles in supporting myelination, synaptic function, and energy metabolism [78–81]. Rapid and targeted transcellular communication through exosomes in the CNS is crucial for optimal brain function. OL-derived exosomes were first found to be internalized by neurons *in vitro* and *in vivo* and to carry major proteins involved in myelination [82,83]. A comprehensive proteomic analysis further revealed that OL-derived exosomes carry a multitude of proteins involved in cellular regulation and cytoskeletal dynamics [84]. The secretion of exosomes from OLs is triggered by activity-dependent release of neuronal glutamate, which binds OL-NMDA and -α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [83]. OL-derived exosomes promote neuronal survival under oxygen-glucose deprivation, elevate action potential firing rate, enhance metabolism, activate pro-survival signaling pathways, and alter gene expression patterns and the transcriptome [83,85]. Therefore, OL-derived exosomes have remarkable potential in supporting neuronal metabolism, function, and health; however, the underlying mechanisms remain largely elusive.

A recent study in mouse neurons revealed that OL-derived exosomes boost axonal mitochondrial bioenergetics by delivering NAD-dependent deacetylase sirtuin 2 (SIRT2) to axons [81]. SIRT2 is undetectable in neurons but highly enriched in mature OLs and released within exosomes [82,84,86]. The transfer of SIRT2 to axons adds an additional layer of deacetylation modification on neuronal mitochondrial proteins. After being released from exosomes within axons, SIRT2 targets mitochondria and deacetylates adenine nucleotide translocase 1 and 2 (ANT1/2) [81] (Figure 2). ANT1/2 play an essential role in bioenergetics by exchanging ADP and ATP across the mitochondrial inner membrane, therefore converting ADP to ATP and catalyzing the export of mitochondrial ATP [87]. ANT1 is acetylated at lysine (Lys) 10, 23, and 92; these positively charged lysines are critical for binding and transport of negatively charged ADP [88]. Acetylation at these lysines neutralizes positive charges, leading to lower binding affinity to ADP and reduced ATP production [89]. SIRT2-dependent deacetylation of ANT1 at Lys23 robustly enhances

ANT1 for ADP binding, thus facilitating the conversion of ADP to ATP [90]. Intriguingly, knockdown of SIRT2 in OLs or deletion of the *sirt2* gene in mice abolishes the OL-axon crosstalk in boosting axonal bioenergetics. Injection of OL-derived exosomes rescues axonal mitochondrial deficiency in the spinal cord of *sirt2* KO mice [81]. These studies provide a new concept that exosome-mediated delivery of SIRT2 from OLs to axons is an efficient and robust mechanism boosting axonal mitochondrial bioenergetics. It remains unknown whether this transcellular crosstalk is regulated in response to axonal energy stress or sustained synaptic activity. It was reported that OLs release EVs by sensing neuronal activity via NMDARs [83]. NMDAR activation also induces GLUT1 expression in the myelin sheath and stimulates production of lactate/pyruvate, thereby supporting axonal energy metabolism during increased synaptic activity [50]. Thus, further investigations are necessary to determine whether SIRT2-filled exosomes are secreted from OLs in response to energetic stress in local axonal compartments. Motor-driven axonal transport is an energy-consuming process [21]. It was recently reported that OL-derived exosomes rescue impaired axonal transport under nutrient deprivation [84]. It remains unclear whether SIRT2 or other energy-signaling molecules mediate this rescue effect.

The composition and secretion of EVs are influenced by the disease progression of neurological disorders [91]. Exosomes can carry and transfer misfolded proteins such as α-synuclein, amyloid precursor protein (APP) and its cleavage products; these pathological forms are associated with neurodegenerative pathology [92]. For example, multiple system atrophy (MSA) is a demyelinating disease characterized by glial inclusions of α-synuclein. A nanoparticle tracking analysis revealed that α-synuclein was significantly lower in OL-derived EVs from the blood of MSA patients than in those with Parkinson's disease. In addition, the concentration of OL-derived exosomes was reduced in MSA patients compared to healthy controls [93]. These suggest that the content and secretion of OL-derived exosomes are likely related to the pathological α-synuclein aggregation in MSA. Glutamate excitotoxicity is a prominent pathophysiological feature of multiple sclerosis (MS) [94]. Pathological glutamate accumulation in experimental autoimmune encephalomyelitis (EAE), an inflammation-driven disease model of MS, can trigger excessive release of exosomes from OLs [83], thus raising an urgent question of whether altered composition and secretion of OL-derived EVs is reflected by or contributes to the disease progression.

Deficient OLs impair axonal energy metabolism in neurological disorders.

A range of neurological disorders are characterized by axonal energetic failure that leads to progressive axonal and neuronal degeneration. In the past two decades, we have witnessed a rapid growth in knowledge of OL-linked axonal pathogenesis [6,7,23,25,30,95–100]. Here we provide a summary of the pathological roles of deficient OLs on axonal energy metabolism (Table 1).

Deficient OLs induce mitochondrial pathology—A wealth of evidence in demyelination models has shown that deficient OLs impair axonal mitochondrial function and trafficking. PLP is the most abundant protein in CNS myelin that is associated with a variety of neurodegenerative diseases, including HSP, SPG2, MS, and others [22–25]. PLP-null mice develop a late-onset axonal degeneration, characterized by mitochondrial

accumulation at distal paranodes [6]. Accumulation of mitochondria at axonal swellings is also involved in several other OL-deficient neurodegeneration models, including mice lacking CNS myelin protein CNP [7] and shiverer mice which harbor a mutation in MBP [9]. These mouse models recapitulate the mitochondrial pathological phenotypes found in human MS patients [95,97,99,100]. The irregular build-up of axonal mitochondria is attributed to impaired transport caused by OL dysfunction. In addition, expression of the axonal mitochondrial anchoring protein SNPH is elevated within chronic MS lesions [97]. SNPH-mediated anchoring is required for the volume increase of axonal mitochondria following demyelination [101]. Notably, deleting SNPH from the shiverer mouse prolongs survival and reduces cerebellar degeneration, presumably by replenishing healthy mitochondria to distal axons [102], suggesting that remobilizing mitochondria benefits axonal energy maintenance. While mitochondrial accumulation is one of the most prominent features of axonal neurodegeneration, whether their bioenergetics are also impaired by deficient OLs remains debatable [9,97,103,104].

Transcellular metabolic signaling in neurodegeneration—OL-derived and MCT1-mediated lactate and pyruvate shuttling provides metabolic support to axons. However, MCT1 expression in OLs is significantly reduced with aging [53]. Loss of MCT1 is observed in human neurodegenerative diseases such as ALS and Creutzfeldt-Jakob disease, and their animal models [23,105]. MCT1 ablation in aging mice leads to axonal degeneration [53]. *Plp*$^{null/y}$ mice display altered myelin structures associated with increased GLUT1 and MCT1; ATP levels in optic nerves from *Plp*$^{null/y}$ mice recover faster and more completely from glucose deprivation [106]. This study highlights that OL-axon metabolite shuttling is enhanced in response to energetic stress, thus protecting axons from degeneration. It remains elusive whether impaired OL-axon metabolite shuttling contributes to axonal energy deficits during neurodegenerative progression. PLP- and CNP-deficient mice develop a secondary progressive axonal degeneration characterized by the formation of axonal swellings. Electron microscopy analysis in PLP-deficient mice demonstrated a 3.6-fold higher number of OL-derived multivesicular bodies (MVBs), which resemble the cytoplasmic storage sites of exosomes before their release. Exosomes are mis-localized in myelinated tracts of PLP- and CNP-deficient mice, and released exosomes are significantly reduced in these models. Consistently, PLP- and CNP-deficient exosomes fail to support axonal transport or neuronal metabolism during nutrient deprivation [84]. This study highlights that OL-axon transcellular signaling through exosomes is a promising therapeutic intervention for protecting axons from neurodegeneration.

CONCLUDING REMARKS

Recent studies have started to uncover the emerging role of transcellular OL-axon metabolic crosstalk in the support of axonal energy metabolism and axonal integrity, which is highly relevant to a range of neurological disorders. These studies also raise several urgent questions to be addressed: (1) whether defective OL-axon energy crosstalk plays a convergent pathological role leading to axonal energy failure and axonal degeneration; (2) whether OLs employ diverse forms of metabolic support across different brain regions where OLs and astrocytes coordinate the glial metabolite provisions to meet the

enhanced energetic demands; (3) whether other exosomal proteins also modulate axonal energy metabolism by targeting to mitochondrial OXPHOS, glycolytic activities, or other bioenergetic pathways; and (4) how OLs sense axonal energy stress or adapt to neuronal signaling under physiological and pathological conditions. Current methodology has limited capacity for labeling and tracing metabolites at the cellular level *in vivo*. Metabolic imaging in higher resolution thus needs to be developed for monitoring transcellular glia-axon metabolic crosstalk. This will advance our understanding of how energy substrates are transferred among OLs, neurons, and astrocytes, and how they are metabolized in axons under physiological and pathological conditions. Future investigations into signaling mechanisms regulating OL-derived metabolic support will benefit the development of therapeutic interventions to restore axonal bioenergetics, and thus protect axons from degeneration.

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REFERENCES

[1]. Barres BA. The mystery and magic of glia: a perspective on their roles in health and disease. Neuron 2008, 60: 430–440. [PubMed: 18995817]

[2]. Stassart RM, Mobius W, Nave KA, and Edgar JM. The Axon-Myelin Unit in Development and Degenerative Disease. Front Neurosci 2018, 12: 467. [PubMed: 30050403]

[3]. McDougall S, Vargas Riad W, Silva-Gotay A, Tavares ER, Harpalani D, Li GL, and Richardson HN. Myelination of Axons Corresponds with Faster Transmission Speed in the Prefrontal Cortex of Developing Male Rats. eNeuro 2018, 5: 0203–0218.

[4]. Lubetzki C, Sol-Foulon N, and Desmazieres A. Nodes of Ranvier during development and repair in the CNS. Nat Rev Neurol 2020, 16: 426–439. [PubMed: 32651566]

[5]. Bonetto G, Belin D, and Karadottir RT. Myelin: A gatekeeper of activity-dependent circuit plasticity? Science 2021, 374: eaba6905. [PubMed: 34618550]

[6]. Griffiths I, Klugmann M, Anderson T, Yool D, Thomson C, Schwab MH, Schneider A, Zimmermann F, McCulloch M, Nadon N, et al. Axonal swellings and degeneration in mice lacking the major proteolipid of myelin. Science 1998, 280: 1610–1613. [PubMed: 9616125]

[7]. Lappe-Siefke C, Goebbels S, Gravel M, Nicksch E, Lee J, Braun PE, Griffiths IR, and Nave KA. Disruption of Cnp1 uncouples oligodendroglial functions in axonal support and myelination. Nat Genet 2003, 33: 366–374. [PubMed: 12590258]

[8]. Loers G, Aboul-Enein F, Bartsch U, Lassmann H, and Schachner M. Comparison of myelin, axon, lipid, and immunopathology in the central nervous system of differentially myelin-compromised mutant mice: a morphological and biochemical study. Mol Cell Neurosci 2004, 27: 175–189. [PubMed: 15485773]

[9]. Andrews H, White K, Thomson C, Edgar J, Bates D, Griffiths I, Turnbull D, and Nichols P. Increased axonal mitochondrial activity as an adaptation to myelin deficiency in the Shiverer mouse. J Neurosci Res 2006, 83: 1533–1539. [PubMed: 16555298]

[10]. Moore S, Meschkat M, Ruhwedel T, Trevisiol A, Tzvetanova ID, Battefeld A, Kusch K, Kole MHP, Strenzke N, Mobius W, et al. A role of oligodendrocytes in information processing. Nat Commun 2020, 11: 5497. [PubMed: 33127910]

[11]. Magistretti PJ, and Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron 2015, 86: 883–901. [PubMed: 25996133]

[12]. Sokoloff L Energetics of functional activation in neural tissues. Neurochem Res 1999, 24: 321–329. [PubMed: 9972882]

[13]. Mews P, Donahue G, Drake AM, Luczak V, Abel T, and Berger SL. Acetyl-CoA synthetase regulates histone acetylation and hippocampal memory. Nature 2017, 546: 381–386. [PubMed: 28562591]

[14]. Karagiannis A, Gallopin T, Lacroix A, Plaisier F, Piquet J, Geoffroy H, Hepp R, Naude J, Le Gac B, Egger R, et al. Lactate is an energy substrate for rodent cortical neurons and enhances their firing activity. Elife 2021, 10. • This study reveals that cortical neurons can uptake and metabolize lactate to enhance spiking activity and neuronal plasticity.

[15]. Silva B, Mantha OL, Schor J, Pascual A, Placais PY, Pavlowsky A, and Preat T. Glia fuel neurons with locally synthesized ketone bodies to sustain memory under starvation. Nat Metab 2022, 4: 213–224. [PubMed: 35177854] • This study shows that Drosophila olfactory neurons uptake and metabolize ketone bodies as an energy substrate to sustain memory formation.

[16]. Yellen G Fueling thought: Management of glycolysis and oxidative phosphorylation in neuronal metabolism. J Cell Biol 2018, 217: 2235–2246. [PubMed: 29752396]

[17]. Ashrafi G, de Juan-Sanz J, Farrell RJ, and Ryan TA. Molecular Tuning of the Axonal Mitochondrial Ca2+ Uniporter Ensures Metabolic Flexibility of Neurotransmission. Neuron 2020, 105: 678–687. [PubMed: 31862210]

[18]. Li S, Xiong GJ, Huang N, and Sheng ZH. The cross-talk of energy sensing and mitochondrial anchoring sustains synaptic efficacy by maintaining presynaptic metabolism. Nat Metab 2020, 2: 1077–1095. [PubMed: 33020662]

[19]. Li S, and Sheng ZH. Energy matters: presynaptic metabolism and the maintenance of synaptic transmission. Nat Rev Neurosci 2022, 23: 4–22. [PubMed: 34782781]

[20]. Harris JJ, Jolivet R, and Attwell D. Synaptic energy use and supply. Neuron 2012, 75: 762–777. [PubMed: 22958818]

[21]. Harris JJ, and Attwell D. The energetics of CNS white matter. J Neurosci 2012, 32: 356–371. [PubMed: 22219296]

[22]. Greer JM, and Pender MP. Myelin proteolipid protein: an effective autoantigen and target of autoimmunity in multiple sclerosis. J Autoimmun 2008, 31: 281–287. [PubMed: 18502611]

[23]. Lee Y, Morrison BM, Li Y, Lengacher S, Farah MH, Hoffman PN, Liu Y, Tsingalia A, Jin L, Zhang PW, et al. Oligodendroglia metabolically support axons and contribute to neurodegeneration. Nature 2012, 487: 443–448. [PubMed: 22801498]

[24]. Novarino G, Fenstermaker AG, Zaki MS, Hofree M, Silhavy JL, Heiberg AD, Abdellateef M, Rosti B, Scott E, Mansour L, et al. Exome sequencing links corticospinal motor neuron disease to common neurodegenerative disorders. Science 2014, 343: 506–511. [PubMed: 24482476]

[25]. Luders KA, Patzig J, Simons M, Nave KA, and Werner HB. Genetic dissection of oligodendroglial and neuronal Plp1 function in a novel mouse model of spastic paraplegia type 2. Glia 2017, 65: 1762–1776. [PubMed: 28836307]

[26]. Nave KA, and Trapp BD. Axon-glial signaling and the glial support of axon function. Annu Rev Neurosci 2008, 31: 535–561. [PubMed: 18558866]

[27]. Saab AS, Tzvetanova ID, and Nave KA. The role of myelin and oligodendrocytes in axonal energy metabolism. Curr Opin Neurobiol 2013, 23: 1065–1072. [PubMed: 24094633]

[28]. Simons M, and Nave KA. Oligodendrocytes: Myelination and Axonal Support. Cold Spring Harb Perspect Biol 2015, 8: a020479. [PubMed: 26101081]

[29]. Philips T, and Rothstein JD. Oligodendroglia: metabolic supporters of neurons. J Clin Invest 2017, 127: 3271–3280. [PubMed: 28862639]

[30]. Mot AI, Depp C, and Nave KA. An emerging role of dysfunctional axono-ligodendrocyte coupling in neurodegenerative diseases. Dialogues Clin Neurosci 2018, 20: 283–292. [PubMed: 30936768]

[31]. Duncan GJ, Simkins TJ, and Emery B. Neuron-Oligodendrocyte Interactions in the Structure and Integrity of Axons. Front Cell Dev Biol 2021, 9: 653101. [PubMed: 33763430]

[32]. Cheng XT, Huang N, and Sheng ZH. Programming axonal mitochondrial maintenance and bioenergetics in neurodegeneration and regeneration. Neuron 2022, 110: 1899–1923. [PubMed:

35429433] •• This review provides an in-depth discussion of how neurons maintain axonal energy metabolism to power neuronal survival and function.

[33]. Ashrafi G, Wu Z, Farrell RJ, and Ryan TA. GLUT4 Mobilization Supports Energetic Demands of Active Synapses. Neuron 2017, 93: 606–615. [PubMed: 28111082]

[34]. Marinangeli C, Didier S, Ahmed T, Caillerez R, Domise M, Laloux C, Begard S, Carrier S, Colin M, Marchetti P, et al. AMP-Activated Protein Kinase Is Essential for the Maintenance of Energy Levels during Synaptic Activation. iScience 2018, 9: 1–13. [PubMed: 30368077]

[35]. Cserep C, Posfai B, Schwarcz AD, and Denes A. Mitochondrial Ultrastructure Is Coupled to Synaptic Performance at Axonal Release Sites. eNeuro 2018, 5: 0390–0317.

[36]. Sheng ZH. The Interplay of Axonal Energy Homeostasis and Mitochondrial Trafficking and Anchoring. Trends Cell Biol 2017, 27: 403–416. [PubMed: 28228333]

[37]. Zhou B, Yu P, Lin MY, Sun T, Chen Y, and Sheng ZH. Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. J Cell Biol 2016, 214: 103–119. [PubMed: 27268498]

[38]. Han Q, Xie Y, Ordaz JD, Huh AJ, Huang N, Wu W, Liu N, Chamberlain KA, Sheng ZH, and Xu XM. Restoring Cellular Energetics Promotes Axonal Regeneration and Functional Recovery after Spinal Cord Injury. Cell Metab 2020, 31: 623–641 e628. [PubMed: 32130884]

[39]. Huang N, Li S, Xie Y, Han Q, Xu XM, and Sheng ZH. Reprogramming an energetic AKT-PAK5 axis boosts axon energy supply and facilitates neuron survival and regeneration after injury and ischemia. Curr Biol 2021, 31: 3098–3114 e3097. [PubMed: 34087103] •• This study elucidates an intrinsic energetic repair signaling axis that boosts axonal energy supply by reprogramming mitochondrial anchoring in response to acute injury-ischemia.

[40]. Ketschek A, Sainath R, Holland S, and Gallo G. The Axonal Glycolytic Pathway Contributes to Sensory Axon Extension and Growth Cone Dynamics. J Neurosci 2021, 41: 6637–6651. [PubMed: 34252036]

[41]. Meyer N, and Rinholm JE. Mitochondria in Myelinating Oligodendrocytes: Slow and Out of Breath? Metabolites 2021, 11. [PubMed: 35050133]

[42]. Chang DT, Honick AS, and Reynolds IJ. Mitochondrial trafficking to synapses in cultured primary cortical neurons. J Neurosci 2006, 26: 7035–7045. [PubMed: 16807333]

[43]. Rinholm JE, Vervaeke K, Tadross MR, Tkachuk AN, Kopek BG, Brown TA, Bergersen LH, and Clayton DA. Movement and structure of mitochondria in oligodendrocytes and their myelin sheaths. Glia 2016, 64: 810–825. [PubMed: 26775288]

[44]. Rintoul GL, Filiano AJ, Brocard JB, Kress GJ, and Reynolds IJ. Glutamate decreases mitochondrial size and movement in primary forebrain neurons. J Neurosci 2003, 23: 7881–7888. [PubMed: 12944518]

[45]. Morland C, Henjum S, Iversen EG, Skrede KK, and Hassel B. Evidence for a higher glycolytic than oxidative metabolic activity in white matter of rat brain. Neurochem Int 2007, 50: 703–709. [PubMed: 17316901]

[46]. Zheng X, Boyer L, Jin M, Mertens J, Kim Y, Ma L, Ma L, Hamm M, Gage FH, and Hunter T. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. Elife 2016, 5.

[47]. Cahoy JD, Emery B, Kaushal A, Foo LC, Zamanian JL, Christopherson KS, Xing Y, Lubischer JL, Krieg PA, Krupenko SA, et al. A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. J Neurosci 2008, 28: 264–278. [PubMed: 18171944]

[48]. Iwata K, Cafe-Mendes CC, Schmitt A, Steiner J, Manabe T, Matsuzaki H, Falkai P, Turck CW, and Martins-de-Souza D. The human oligodendrocyte proteome. Proteomics 2013, 13: 3548–3553. [PubMed: 24167090]

[49]. Ding J, Ji J, Rabow Z, Shen T, Folz J, Brydges CR, Fan S, Lu X, Mehta S, Showalter MR, et al. A metabolome atlas of the aging mouse brain. Nat Commun 2021, 12: 6021. [PubMed: 34654818]

[50]. Saab AS, Tzvetavona ID, Trevisiol A, Baltan S, Dibaj P, Kusch K, Mobius W, Goetze B, Jahn HM, Huang W, et al. Oligodendroglial NMDA Receptors Regulate Glucose Import and Axonal Energy Metabolism. Neuron 2016, 91: 119–132. [PubMed: 27292539]

[51]. Funfschilling U, Supplie LM, Mahad D, Boretius S, Saab AS, Edgar J, Brinkmann BG, Kassmann CM, Tzvetanova ID, Mobius W, et al. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 2012, 485: 517–521. [PubMed: 22622581]

[52]. Lai LM, Gropman AL, and Whitehead MT. MR Neuroimaging in Pediatric Inborn Errors of Metabolism. Diagnostics (Basel) 2022, 12: 861. [PubMed: 35453911]

[53]. Philips T, Mironova YA, Jouroukhin Y, Chew J, Vidensky S, Farah MH, Pletnikov MV, Bergles DE, Morrison BM, and Rothstein JD. MCT1 Deletion in Oligodendrocyte Lineage Cells Causes Late-Onset Hypomyelination and Axonal Degeneration. Cell Rep 2021, 34: 108610. [PubMed: 33440165] •• This study shows that loss of oligodendrocyte-specific MCT1 during aging leads to significant axonal degeneration with concomitant hypomyelination.

[54]. Lassetter AP, Corty MM, Barria R, Sheehan AE, Hill JQ, Aicher SA, Fox AN, and Freeman MR. Glial TGFbeta activity promotes neuron survival in peripheral nerves. J Cell Biol 2023, 222: e202111053. [PubMed: 36399182]

[55]. McIlwain H, and Gore MB. Induced loss in cerebral tissues of respiratory response to electrical impulses, and its partial restoration by additional substrates. Biochem J 1953, 54: 305–312. [PubMed: 13058876]

[56]. Boumezbeur F, Petersen KF, Cline GW, Mason GF, Behar KL, Shulman GI, and Rothman DL. The contribution of blood lactate to brain energy metabolism in humans measured by dynamic 13C nuclear magnetic resonance spectroscopy. J Neurosci 2010, 30: 13983–13991. [PubMed: 20962220]

[57]. Glenn TC, Martin NA, Horning MA, McArthur DL, Hovda DA, Vespa P, and Brooks GA. Lactate: brain fuel in human traumatic brain injury: a comparison with normal healthy control subjects. J Neurotrauma 2015, 32: 820–832. [PubMed: 25594628]

[58]. Wyss MT, Jolivet R, Buck A, Magistretti PJ, and Weber B. In vivo evidence for lactate as a neuronal energy source. J Neurosci 2011, 31: 7477–7485. [PubMed: 21593331]

[59]. Tekkok SB, Brown AM, Westenbroek R, Pellerin L, and Ransom BR. Transfer of glycogen-derived lactate from astrocytes to axons via specific monocarboxylate transporters supports mouse optic nerve activity. J Neurosci Res 2005, 81: 644–652. [PubMed: 16015619]

[60]. Trevisiol A, Saab AS, Winkler U, Marx G, Imamura H, Mobius W, Kusch K, Nave KA, and Hirrlinger J. Monitoring ATP dynamics in electrically active white matter tracts. Elife 2017, 6: e24241. [PubMed: 28414271]

[61]. Panov A, Orynbayeva Z, Vavilin V, and Lyakhovich V. Fatty acids in energy metabolism of the central nervous system. Biomed Res Int 2014, 2014: 472459. [PubMed: 24883315]

[62]. Barber CN, and Raben DM. Lipid Metabolism Crosstalk in the Brain: Glia and Neurons. Front Cell Neurosci 2019, 13: 212. [PubMed: 31164804]

[63]. Schonfeld P, and Reiser G. Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain. J Cereb Blood Flow Metab 2013, 33: 1493–1499. [PubMed: 23921897]

[64]. Thevenet J, De Marchi U, Domingo JS, Christinat N, Bultot L, Lefebvre G, Sakamoto K, Descombes P, Masoodi M, and Wiederkehr A. Medium-chain fatty acids inhibit mitochondrial metabolism in astrocytes promoting astrocyte-neuron lactate and ketone body shuttle systems. FASEB J 2016, 30: 1913–1926. [PubMed: 26839375]

[65]. Dimas P, Montani L, Pereira JA, Moreno D, Trotzmuller M, Gerber J, Semenkovich CF, Kofeler HC, and Suter U. CNS myelination and remyelination depend on fatty acid synthesis by oligodendrocytes. Elife 2019, 8: e44702. [PubMed: 31063129]

[66]. Asadollahi E AT, AS Saab, ZJ Looser, P Dibaj, K Kusch, T Ruhwedel, O Jahn, M Baes, B Weber, et al. Myelin lipids as nervous system energy reserves. bioRxiv 2022, 10.1101/2022.02.24.481621. • This study shows that oligodendrocytes break down myelin compartments and utilize myelin lipids as an energy substrate to support axonal energy metabolism during glucose deprivation.

[67]. Crane PK, Walker R, Hubbard RA, Li G, Nathan DM, Zheng H, Haneuse S, Craft S, Montine TJ, Kahn SE, et al. Glucose levels and risk of dementia. N Engl J Med 2013, 369: 540–548. [PubMed: 23924004]

[68]. Gordon BA, Blazey TM, Su Y, Hari-Raj A, Dincer A, Flores S, Christensen J, McDade E, Wang G, Xiong C, et al. Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: a longitudinal study. Lancet Neurol 2018, 17: 241–250. [PubMed: 29397305]

[69]. Wang W, Zhao F, Ma X, Perry G, and Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener 2020, 15: 30. [PubMed: 32471464]

[70]. Klosinski LP, Yao J, Yin F, Fonteh AN, Harrington MG, Christensen TA, Trushina E, and Brinton RD. White Matter Lipids as a Ketogenic Fuel Supply in Aging Female Brain: Implications for Alzheimer's Disease. EBioMedicine 2015, 2: 1888–1904. [PubMed: 26844268]

[71]. Griemsmann S, Hoft SP, Bedner P, Zhang J, von Staden E, Beinhauer A, Degen J, Dublin P, Cope DW, Richter N, et al. Characterization of Panglial Gap Junction Networks in the Thalamus, Neocortex, and Hippocampus Reveals a Unique Population of Glial Cells. Cereb Cortex 2015, 25: 3420–3433. [PubMed: 25037920]

[72]. Belanger M, Allaman I, and Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 2011, 14: 724–738. [PubMed: 22152301]

[73]. Machler P, Wyss MT, Elsayed M, Stobart J, Gutierrez R, von Faber-Castell A, Kaelin V, Zuend M, San Martin A, Romero-Gomez I, et al. In Vivo Evidence for a Lactate Gradient from Astrocytes to Neurons. Cell Metab 2016, 23: 94–102. [PubMed: 26698914]

[74]. Matsui T, Omuro H, Liu YF, Soya M, Shima T, McEwen BS, and Soya H. Astrocytic glycogen-derived lactate fuels the brain during exhaustive exercise to maintain endurance capacity. Proc Natl Acad Sci U S A 2017, 114: 6358–6363. [PubMed: 28515312]

[75]. Rouach N, Koulakoff A, Abudara V, Willecke K, and Giaume C. Astroglial metabolic networks sustain hippocampal synaptic transmission. Science 2008, 322: 1551–1555. [PubMed: 19056987]

[76]. Philippot C, Griemsmann S, Jabs R, Seifert G, Kettenmann H, and Steinhauser C. Astrocytes and oligodendrocytes in the thalamus jointly maintain synaptic activity by supplying metabolites. Cell Rep 2021, 34: 108642. [PubMed: 33472059] • This study shows that astrocytes and oligodendrocytes exchange glucose and pyruvate though MCT and connexin channels to support neuronal activity.

[77]. van Niel G, D'Angelo G, and Raposo G. Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 2018, 19: 213–228. [PubMed: 29339798]

[78]. Fruhbeis C, Frohlich D, and Kramer-Albers EM. Emerging roles of exosomes in neuron-glia communication. Front Physiol 2012, 3: 119. [PubMed: 22557979]

[79]. Goncalves MB, Wu Y, Clarke E, Grist J, Hobbs C, Trigo D, Jack J, and Corcoran JPT. Regulation of Myelination by Exosome Associated Retinoic Acid Release from NG2-Positive Cells. J Neurosci 2019, 39: 3013–3027. [PubMed: 30760627]

[80]. Gharbi T, Zhang Z, and Yang GY. The Function of Astrocyte Mediated Extracellular Vesicles in Central Nervous System Diseases. Front Cell Dev Biol 2020, 8: 568889. [PubMed: 33178687]

[81]. Chamberlain KA, Huang N, Xie Y, LiCausi F, Li S, Li Y, and Sheng ZH. Oligodendrocytes enhance axonal energy metabolism by deacetylation of mitochondrial proteins through transcellular delivery of SIRT2. Neuron 2021, 109: 3456–3472 e3458. [PubMed: 34506725] •• This study reveals a new transcellular oligodendrocyte-to-axon signaling that boosts axonal mitochondrial bioenergetics by delivering SIRT2 to neurons.

[82]. Kramer-Albers EM, Bretz N, Tenzer S, Winterstein C, Mobius W, Berger H, Nave KA, Schild H, and Trotter J. Oligodendrocytes secrete exosomes containing major myelin and stress-protective proteins: Trophic support for axons? Proteomics Clin Appl 2007, 1: 1446–1461. [PubMed: 21136642]

[83]. Fruhbeis C, Frohlich D, Kuo WP, Amphornrat J, Thilemann S, Saab AS, Kirchhoff F, Mobius W, Goebbels S, Nave KA, et al. Neurotransmitter-triggered transfer of exosomes mediates oligodendrocyte-neuron communication. PLoS Biol 2013, 11: e1001604. [PubMed: 23874151]

[84]. Fruhbeis C, Kuo-Elsner WP, Muller C, Barth K, Peris L, Tenzer S, Mobius W, Werner HB, Nave KA, Frohlich D, et al. Oligodendrocytes support axonal transport and maintenance via exosome secretion. PLoS Biol 2020, 18: e3000621. [PubMed: 33351792] •• This study reveals that oligodendroglial exosomes rescue impaired axonal transport under nutrient deprivation.

[85]. Frohlich D, Kuo WP, Fruhbeis C, Sun JJ, Zehendner CM, Luhmann HJ, Pinto S, Toedling J, Trotter J, and Kramer-Albers EM. Multifaceted effects of oligodendroglial exosomes on neurons: impact on neuronal firing rate, signal transduction and gene regulation. Philos Trans R Soc Lond B Biol Sci 2014, 369: 20130510. [PubMed: 25135971]

[86]. Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N, et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci 2014, 34: 11929–11947. [PubMed: 25186741]

[87]. Bround MJ, Bers DM, and Molkentin JD. A 20/20 view of ANT function in mitochondrial biology and necrotic cell death. J Mol Cell Cardiol 2020, 144: A3–A13. [PubMed: 32454061]

[88]. Kim SC, Sprung R, Chen Y, Xu Y, Ball H, Pei J, Cheng T, Kho Y, Xiao H, Xiao L, et al. Substrate and functional diversity of lysine acetylation revealed by a proteomics survey. Mol Cell 2006, 23: 607–618. [PubMed: 16916647]

[89]. Mielke C, Lefort N, McLean CG, Cordova JM, Langlais PR, Bordner AJ, Te JA, Ozkan SB, Willis WT, and Mandarino LJ. Adenine nucleotide translocase is acetylated in vivo in human muscle: Modeling predicts a decreased ADP affinity and altered control of oxidative phosphorylation. Biochemistry 2014, 53: 3817–3829. [PubMed: 24884163]

[90]. Liu G, Park SH, Imbesi M, Nathan WJ, Zou X, Zhu Y, Jiang H, Parisiadou L, and Gius D. Loss of NAD-Dependent Protein Deacetylase Sirtuin-2 Alters Mitochondrial Protein Acetylation and Dysregulates Mitophagy. Antioxid Redox Signal 2017, 26: 849–863. [PubMed: 27460777]

[91]. Soria FN, Pampliega O, Bourdenx M, Meissner WG, Bezard E, and Dehay B. Exosomes, an Unmasked Culprit in Neurodegenerative Diseases. Front Neurosci 2017, 11: 26. [PubMed: 28197068]

[92]. Hornung S, Dutta S, and Bitan G. CNS-Derived Blood Exosomes as a Promising Source of Biomarkers: Opportunities and Challenges. Front Mol Neurosci 2020, 13: 38. [PubMed: 32265650]

[93]. Yu Z, Shi M, Stewart T, Fernagut PO, Huang Y, Tian C, Dehay B, Atik A, Yang D, De Giorgi F, et al. Reduced oligodendrocyte exosome secretion in multiple system atrophy involves SNARE dysfunction. Brain 2020, 143: 1780–1797. [PubMed: 32428221]

[94]. Pitt D, Werner P, and Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. Nat Med 2000, 6: 67–70. [PubMed: 10613826]

[95]. Garbern JY, Yool DA, Moore GJ, Wilds IB, Faulk MW, Klugmann M, Nave KA, Sistermans EA, van der Knaap MS, Bird TD, et al. Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. Brain 2002, 125: 551–561. [PubMed: 11872612]

[96]. Edgar JM, McLaughlin M, Yool D, Zhang SC, Fowler JH, Montague P, Barrie JA, McCulloch MC, Duncan ID, Garbern J, et al. Oligodendroglial modulation of fast axonal transport in a mouse model of hereditary spastic paraplegia. J Cell Biol 2004, 166: 121–131. [PubMed: 15226307]

[97]. Mahad DJ, Ziabreva I, Campbell G, Lax N, White K, Hanson PS, Lassmann H, and Turnbull DM. Mitochondrial changes within axons in multiple sclerosis. Brain 2009, 132: 1161–1174. [PubMed: 19293237]

[98]. Traka M, Arasi K, Avila RL, Podojil JR, Christakos A, Miller SD, Soliven B, and Popko B. A genetic mouse model of adult-onset, pervasive central nervous system demyelination with robust remyelination. Brain 2010, 133: 3017–3029. [PubMed: 20851998]

[99]. Nikic I, Merkler D, Sorbara C, Brinkoetter M, Kreutzfeldt M, Bareyre FM, Bruck W, Bishop D, Misgeld T, and Kerschensteiner M. A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med 2011, 17: 495–499. [PubMed: 21441916]

[100]. Zambonin JL, Zhao C, Ohno N, Campbell GR, Engeham S, Ziabreva I, Schwarz N, Lee SE, Frischer JM, Turnbull DM, et al. Increased mitochondrial content in remyelinated axons: implications for multiple sclerosis. Brain 2011, 134: 1901–1913. [PubMed: 21705418]

[101]. Ohno N, Chiang H, Mahad DJ, Kidd GJ, Liu L, Ransohoff RM, Sheng ZH, Komuro H, and Trapp BD. Mitochondrial immobilization mediated by syntaphilin facilitates survival of demyelinated axons. Proc Natl Acad Sci U S A 2014, 111: 9953–9958. [PubMed: 24958879]

[102]. Joshi DC, Zhang CL, Lin TM, Gusain A, Harris MG, Tree E, Yin Y, Wu C, Sheng ZH, Dempsey RJ, et al. Deletion of mitochondrial anchoring protects dysmyelinating shiverer: implications for progressive MS. J Neurosci 2015, 35: 5293–5306. [PubMed: 25834054]

[103]. Bristow EA, Griffiths PG, Andrews RM, Johnson MA, and Turnbull DM. The distribution of mitochondrial activity in relation to optic nerve structure. Arch Ophthalmol 2002, 120: 791–796. [PubMed: 12049585]

[104]. Yin X, Kidd GJ, Ohno N, Perkins GA, Ellisman MH, Bastian C, Brunet S, Baltan S, and Trapp BD. Proteolipid protein-deficient myelin promotes axonal mitochondrial dysfunction via altered metabolic coupling. J Cell Biol 2016, 215: 531–542. [PubMed: 27872255]

[105]. Andres Benito P, Dominguez Gonzalez M, and Ferrer I. Altered gene transcription linked to astrocytes and oligodendrocytes in frontal cortex in Creutzfeldt-Jakob disease. Prion 2018, 12: 216–225. [PubMed: 30009661]

[106]. Trevisiol A, Kusch K, Steyer AM, Gregor I, Nardis C, Winkler U, Kohler S, Restrepo A, Mobius W, Werner HB, et al. Structural myelin defects are associated with low axonal ATP levels but rapid recovery from energy deprivation in a mouse model of spastic paraplegia. PLoS Biol 2020, 18: e3000943. [PubMed: 33196637] • This study shows that Plpnull/y mice exhibit lower basal axonal ATP levels and reduced compound action potential amplitudes in electrically active optic nerves.

[107]. Dutta R, McDonough J, Yin X, Peterson J, Chang A, Torres T, Gudz T, Macklin WB, Lewis DA, Fox RJ, et al. Mitochondrial dysfunction as a cause of axonal degeneration in multiple sclerosis patients. Ann Neurol 2006, 59: 478–489. [PubMed: 16392116]

[108]. Hogan V, White K, Edgar J, McGill A, Karim S, McLaughlin M, Griffiths I, Turnbull D, and Nichols P. Increase in mitochondrial density within axons and supporting cells in response to demyelination in the Plp1 mouse model. J Neurosci Res 2009, 87: 452–459. [PubMed: 18803300]

Highlights

- Neurons adopt special mechanisms maintaining local ATP supply in distal axons
- Oligodendrocytes provide metabolic support to axons by shuttling metabolites
- Oligodendrocytes release exosomes to boost axonal mitochondrial bioenergetics
- Deficient oligodendrocytes impair axonal energy metabolism in neurodegeneration

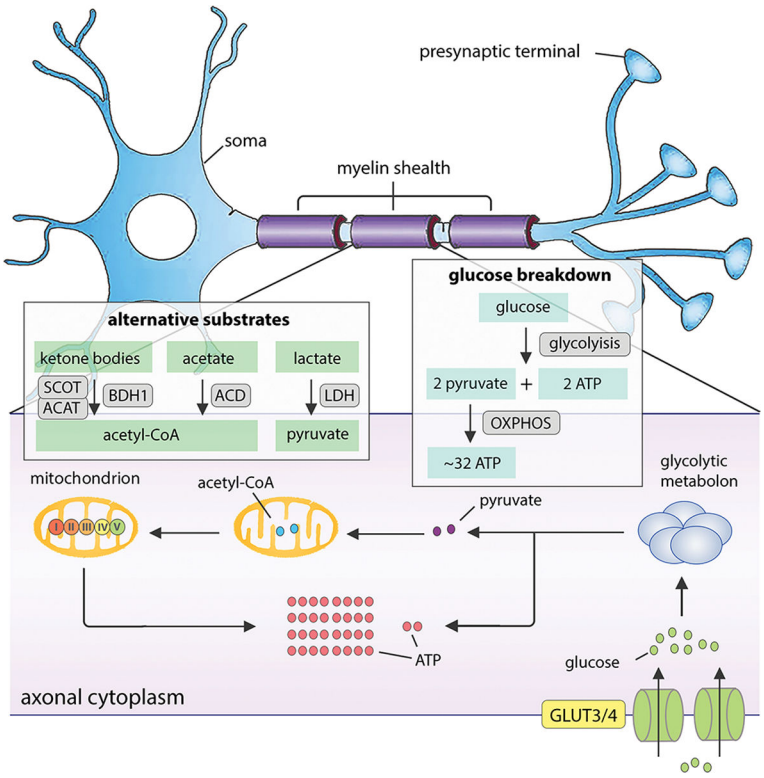

Figure 1. Energy metabolism in axons.

Glucose is the predominant carbon source for synthesizing adenosine triphosphate (ATP). Glucose uptake into the axonal cytoplasm occurs via the major neuronal glucose transporters GLUT3/4. Glycolysis converts one glucose molecule into two pyruvate molecules, with a net production of two ATP molecules. Under aerobic conditions, these pyruvate molecules are subsequently transferred into the mitochondrion for entry into the tricarboxylic acid cycle, where they are converted into acetyl-CoA molecules to fuel oxidative phosphorylation (OXPHOS), leading to a net production of ~32 ATP molecules. The complete oxidation of glucose by the combined action of glycolysis and OXPHOS is the most efficient bioenergetic source of the cellular ATP that maintains axonal energy homeostasis. When glucose availability in axons is limited, other metabolites, such as lactate, acetate, and ketone bodies, serve as alternative energy substrates for axonal ATP synthesis. Lactate is converted to pyruvate by lactate dehydrogenase (LDH). Acetate activation to acetyl-CoA is catalyzed by the ADP-forming acetyl-CoA synthetase (ACD). Although glial ketogenesis in supporting axonal energy metabolism requires further validation in neuronal systems, ketone bodies could be oxidized to acetyl-CoA molecules through a series of enzymatic reactions involving d-3-Hydroxy-n-butyrate dehydrogenase (BDH1), 3-oxoacid CoA-transferase (SCOT), and acetyl-CoA acetyltransferase (ACAT). Through conversion to pyruvate or acetyl-CoA molecules, these alternative metabolic substrates could enter OXPHOS within mitochondria for ATP generation to maintain axonal energy metabolism.

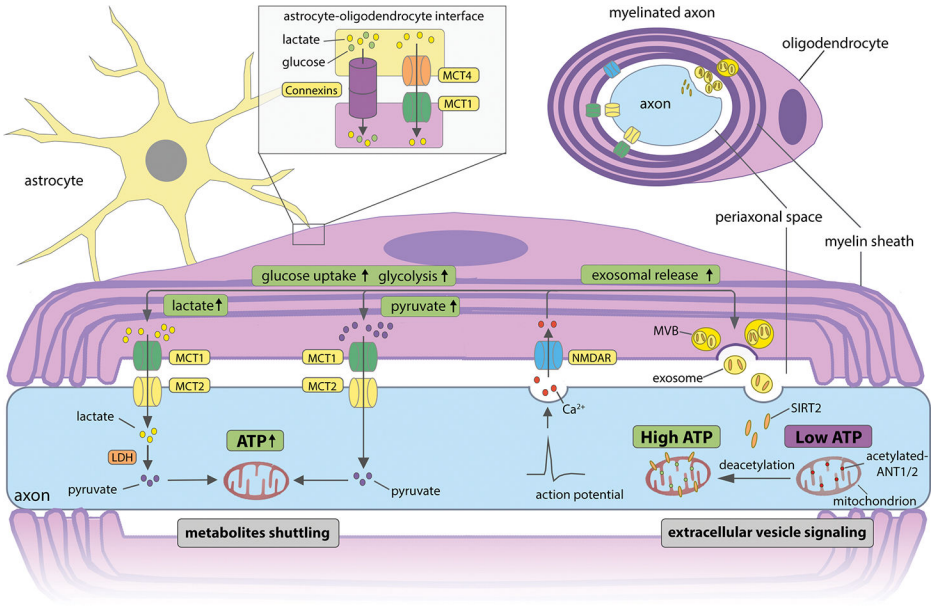

Figure 2. Transcellular metabolite shuttling and metabolic signaling between oligodendrocytes and neurons.

Oligodendrocytes (OLs) and neurons exhibit large diversity in transcriptomic, proteomic, and metabolomic landscapes, and thus OLs serve as an ideal metabolic supplement for axonal energy production by providing metabolites and proteins that are in short supply in neurons through two pathways: (1) shuttling energy substrates, such as lactate and pyruvate, that can fuel axonal energy metabolism and (2) secreting exosomes containing proteins and RNAs that can boost neuronal energy metabolism. Mature OLs are highly glycolytic; the glycolytic end products pyruvate and lactate can pass from OLs to axons through the myelinic monocarboxylate transporter 1 (MCT1) and its neuronal isoform MCT2. After entering axons, lactate is converted to pyruvate by LDH in the axon cytoplasm. Pyruvate fuel mitochondria ATP production to support axonal energy metabolism. In addition, astrocytes participate in metabolite shuttling between OLs and axons. Astrocytes are highly glycolytic and almost exclusively store brain glycogen, where glycogen is broken down to glucose, which is metabolized by glycolysis to produce pyruvate and lactate. Astrocyte-derived glucose and lactate/pyruvate are transported to OLs through gradient-diffusion along MCTs and/or connexin channels between the astrocyte-OL interface, thus maintaining the metabolite shuttling pathway when glucose availability is restricted. OLs also release exosomes containing proteins, lipids, and RNA molecules to support axonal energy metabolism. One of these components within OL-derived exosomes is NAD-dependent deacetylase sirtuin 2 (SIRT2), which is undetectable in neurons but highly enriched in mature OLs and released within exosomes. After being released from exosomes within axons, SIRT2 targets mitochondria and deacetylates adenine nucleotide translocase 1 and 2 (ANT1/2). SIRT2-dependent deacetylation of ANT1 robustly enhances ANT1's affinity for ADP binding, facilitating the conversion of ADP to ATP and the export of mitochondrial ATP. Thus, transcellular OL-axon metabolic signaling is critical for maintaining or boosting axonal bioenergetics. OLs release exosomes by sensing neuronal activity via NMDARs in the myelinating processes of OLs. NMDAR activation also induces GLUT1 expression

in the myelin sheath, resulting in increased glucose uptake and glycolytic activity, which eventually enhances gradient-based shuttling of pyruvate and lactate from OLs to axons. These pathways allow neurons to maintain axonal energy homeostasis and fulfill activity-enhanced energy demand.

Table 1.

Axonal mitochondrial phenotypes in rodent and human disease models associated with deficient OLs.

OL-deficient models	Metabolic phenotypes	Refs
PLP-DM20-deficient mice	Focal axonal swellings containing mitochondria in white and gray matter from the age of 6–8 weeks.	[6]
PLP1-deficient patient	Axonal swellings with accumulated mitochondria.	[95]
Postmortem human optic nerve	High cytochrome-c oxidase activity in unmyelinated regions.	[103]
Cnp1-null mice	Mitochondrial accumulation at axonal swellings of spinal cord.	[7]
Shiverer mice (MBP-null)	Increased mitochondrial activity and number within dysmyelinated axons.	[9]
MS patient motor cortex	Reduced mitochondrial gene expression and respiratory chain activity.	[107]
Pattern III MS	Defects in respiratory chain complex IV in axons.	[97]
Active chronic MS	Reduced complex IV activity.	[97]
Inactive chronic MS	Mitochondrial accumulation at axonal swellings and higher complex IV activity in large diameter axons.	[97]
Plp1-overexpressing mice	Increased mitochondrial density in spinal cord axons.	[108]
Diphtheria Toxin subunit A mice	Increased mitochondria numbers in demyelinated axons.	[98]
Spinal experimental encephalomyelitis lesions	Swollen mitochondria in focal axonal degeneration.	[99]
MCT1 heterozygous KO mice	Swollen and enlarged mitochondria in optic nerve.	[23]
P_0-CNS mice (expressing P_0 instead of PLP in CNS myelin)	Lower axonal ATP levels in optic nerve.	[104]
Plp$^{null/y}$ mice	Increased GLUT1 and MCT1 and faster recovery of ATP levels upon reperfusion of glucose.	[106]
OL-specific MCT1 KO	Enlarged mitochondria with irregular cristae structure.	[53]