Neurotherapeutics (2021) 18:2185–2199
https://doi.org/10.1007/s13311-021-01150-2

REVIEW

Metabolic Transporters in the Peripheral Nerve—What, Where, and Why?

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Accepted: 21 October 2021 / Published online: 12 November 2021

Abstract

Cellular metabolism is critical not only for cell survival, but also for cell fate, function, and intercellular communication. There are several different metabolic transporters expressed in the peripheral nervous system, and they each play important roles in maintaining cellular energy. The major source of energy in the peripheral nervous system is glucose, and glucose transporters 1 and 3 are expressed and allow blood glucose to be imported and utilized by peripheral nerves. There is also increasing evidence that other sources of energy, particularly monocarboxylates such as lactate that are transported primarily by monocarboxylate transporters 1 and 2 in peripheral nerves, can be efficiently utilized by peripheral nerves. Finally, emerging evidence supports an important role for connexins and possibly pannexins in the supply and regulation of metabolic energy. In this review, we will first define these critical metabolic transporter subtypes and then examine their localization in the peripheral nervous system. We will subsequently discuss the evidence, which comes both from experiments in animal models and observations from human diseases, supporting critical roles played by these metabolic transporters in the peripheral nervous system. Despite progress made in understanding the function of these transporters, many questions and some discrepancies remain, and these will also be addressed throughout this review. Peripheral nerve metabolism is fundamentally important and renewed interest in these pathways should help to answer many of these questions and potentially provide new treatments for neurologic diseases that are partly, or completely, caused by disruption of metabolism.

Keywords Metabolism · Peripheral nervous system (PNS) · Schwann cells (SC) · Motor neurons · Sensory neurons · Dorsal root ganglia (DRG) · Monocarboxylate transporters (MCT) · Glucose transporters (GLUT) · Connexin · Pannexin

Introduction

> "Nobody realizes that some people expend tremendous energy merely to be normal."
> Albert Camus, Notebooks 1942–1951 [1]

Peripheral nerves are highly metabolically active, requiring energy to maintain electrochemical gradients necessary for action potential propagation, axon transport, and production of neurochemicals, among other functions. Carbohydrates, specifically glucose and lactate, are the primary energy source to fulfill their energy requirements [2]. The fully developed human brain, which is approximately 2% of the body weight, uses ~20% of glucose-derived energy and requires continuous delivery of energy metabolites from the blood [3]. To maintain a constant supply of energy, multiple metabolic transporters are required. The primary transporters in the peripheral nervous system (PNS) are glucose transporters (GLUTs) and monocarboxylate transporters (MCTs), though connexins, and possibly pannexins, may also play a role [4–8]. There are several unique features to the PNS that make its energy needs different from the central nervous system (CNS). First, compared to the CNS blood–brain barrier, the PNS has a less restrictive blood-nerve barrier (BNB), which is composed of the perineurium and endoneurial blood vessels [9]. In fact, the BNB is even more permeable in the dorsal root ganglia (DRG) and nerve terminals, allowing greater access of blood cells, proteins, and electrolytes to DRG neuronal cell bodies [10] and axon terminals innervating sensory end organs in the skin and neuromuscular junctions in the muscle [11]. Additionally, the permeability of BNB is altered in cases of nerve injury and peripheral neuropathies, including diabetic peripheral

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neuropathy, where leakage of harmful molecules in and around the nerve tissue and classical cytokine and interleukin-mediated inflammation potentially contribute to nerve injury [12]. Second, peripheral axons are extremely long compared to CNS axons, with some extending up to 1 m from the motor neuron or DRG neuron cell bodies. Thus, it is impractical for distal components of the axon to receive their metabolic energy exclusively from the cell body, necessitating mechanisms for local energy supply to the distal axon. Third, some peripheral axons are surrounded by myelin, which is a hydrophobic barrier produced by Schwann cells (SC) that excludes polar molecules such as carbohydrates from reaching the axon [13]. To compensate for this, specific metabolic and other transporters exist in channels within the myelin sheaths of PNS nerves, termed Schmidt-Lanterman incisures, to allow access of extracellular solutes to the axon and a path for dispersing axon waste products [14]. Over the last several years, our knowledge about the localization and function of metabolic transporters in the PNS has grown considerably and we are just beginning to discover their contribution to normal physiology and pathologic conditions.

What Are the Different Types of Metabolic Transporters?

Glucose Transporters

All mammalian cells require glucose as a metabolic substrate. It is transported across the cell membrane by facilitative diffusion mediated by members of the GLUT family [15]. Most of the GLUTs catalyze the ATP-independent bidirectional transfer of glucose across membranes, though low intracellular glucose levels in most cells produce primarily glucose import (Fig. 1). There are 14 members of the GLUT family [16], expressed by different cell types in the nervous system [17]. These transporters possess 12 membrane spanning domains creating internal as well as external ligand-binding sites at the N- and C-terminal cytoplasmic domains with glycosylation on one of the extracellular sites. The plasma membrane glucose transporters of this family are designated as GLUT1-4 [18, 19]. GLUT5 is a transporter of fructose [20]. GLUT6 is a nonfunctional pseudogene [21], while GLUT7 is a hepatic endoplasmic reticulum glucose transporter [22]. The

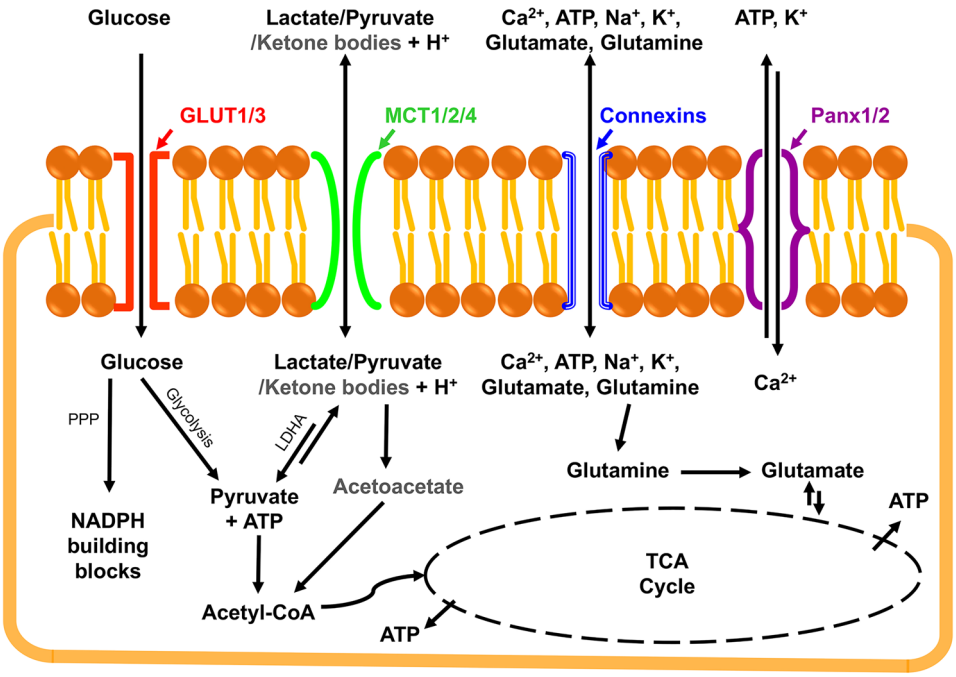

Fig. 1 Metabolic transporter in the peripheral nervous system. The major transporters are glucose transporters (GLUT) 1 and 3 and monocarboxylate transporters (MCT) 1, 2, and 4. GLUT1 and 3 transport glucose into the cell where it can be metabolized by glycolysis or the pentose phosphate pathway (PPP). MCTs co-transport lactate, pyruvate, or ketone bodies along with a proton (H^+) either into or out of cells, based on their concentration gradients. Lactate, pyruvate, and ketone bodies can be substrates for the tricarboxylic acid (TCA) cycle to produce ATP through oxidative metabolism. Additional transporter are connexins (Cx) and pannexins (Panx), specifically Panx1 and 2. Cx have been shown to transport a number of products through gap junctions or hemichannels, primarily limited only by size, including ATP, ions, glutamate, and glutamine. Panx1 and 2 transport ATP and ions through hemichannels into or out of cells

function of other GLUT family member has not yet been determined. The distribution and features of the GLUT transporters, GLUT1 and GLUT3, are considered together because their expression is dependent on both glucose and hypoxia and both play a key role in delivery of glucose in the nervous system [8]. GLUT1 and GLUT3 are both upregulated by circulating glucose [23, 24] and hypoxic conditions through hypoxia-inducible factor 1α (HIF-1α)-mediated transcriptional activation [25]. The regulation of GLUT expression appears to occur at the transcriptional, posttranscriptional, and posttranslational levels. The localization of GLUT1 and GLUT3 to the nodal and paranodal regions of peripheral nerves and response to glucose concentrations and hypoxic conditions suggest that they play a critical role in PNS energy metabolism.

Though not expressed in the PNS, the other glucose transporters have some interesting features that my impact PNS diseases. GLUT2 is the primary transporter in the liver, where it participates in gluconeogenesis, which is important for maintaining stable glucose levels for the CNS and PNS in times of starvation [26, 27]. GLUT4 is the transporter responsive to the master glucose regulatory hormone—insulin. Insulin stimulates the uptake of glucose from the blood in several tissues by facilitated diffusion through GLUT4, though the primary sites are cardiac muscle, skeletal muscle, and fat [28]. GLUT4 is associated with specific membrane vesicles inside the cell and translocated to the plasma membrane following binding of insulin to its receptor [29]. Through this mechanism, these tissues are able to take up glucose from the blood, maintaining serum glucose in a safe range. In diabetes, where there is either failure to produce insulin or insensitivity of insulin receptors, GLUT4 is not mobilized, which leads to elevated blood sugars. Studies in animals and humans indicate that alterations in GLUT4 expression, trafficking, and/or activity occur in adipose cells and muscle in diabetes and other insulin-resistant states [30–32]. GLUT1 and GLUT3 are not regulated by insulin [33]. In the setting of elevated blood sugars, these transporters will import high amounts of glucose into neurons and SCs, leading to toxicity through a variety of downstream pathways [34]. Though GLUT1 is not regulated by insulin, it has recently been shown that GLUT1 translocation to the cell surface of oligodendrocytes and into myelin membranes is regulated by N-methyl-D-aspartate (NMDA) receptor stimulation [35]. Although slower, the translocation itself is reminiscent of GLUT4 trafficking in muscle cells or adipocytes in response to insulin signaling and demonstrates that surface expression of GLUT1 can also be regulated. Interestingly, SCs do express insulin receptors, which modulate the production of myelin and thus may contribute to diabetic peripheral neuropathy through mechanisms independent of GLUT1 [36, 37].

Monocarboxylate Transporters

MCTs, which are encoded by the gene class, *SLC16A*, are predicted to consist of 12 transmembrane helices with C- and N-termini located within the cytoplasm. The helices are arranged in two six helix bundles that are linked by a large intracellular loop between transmembranes 6 and 7 [38]. Although 14 members of the MCT family have been identified based on sequence homology and protein structure, the conserved sequence among different isoforms in mammals is highest for MCT1–4, whereas sequences of other family members are less conserved. Each isoform is distinguished by kinetic properties, tissue distribution, and substrate specificity. MCT1–4 are the only isoforms that have been shown experimentally to transport monocarboxylates [39], and this transport is bidirectional and electroneutral with the co-transport of monocarboxylate along with a proton in a 1:1 ratio (Fig. 1). Each isoform has different affinities and kinetics for the various monocarboxylates, which include L-lactate, pyruvate, and ketone bodies. The net direction of this facilitated diffusion is dependent on the relative intra- and extracellular concentration gradients of protons and monocarboxylates across the plasma membrane and no energy is required. The regulation of MCT expression is via both transcriptional and post-transcriptional mechanisms [40]. MCTs form associations with one of two proteins of the immunoglobulin superfamily, namely, embigin and basigin, that are crucial for intracellular trafficking. Basigin is the preferred binding partner for MCT1; in contrast, expression of MCT2 in the plasma membrane requires co-expression with embigin [41]. MCT1 is the best studied and functionally characterized isoform of the MCT family and has the widest tissue distribution. In addition to the PNS, where it is the most highly expressed transporter [5], it is ubiquitously expressed in the heart, brain, liver, kidney, intestine, muscles, white adipose tissue, testes, placenta, red blood cells, and immune cells, including lymphocytes and monocytes [42]. MCT2 and MCT4 are also expressed in the PNS, though at lower levels compared to MCT1 [4].

MCTs are responsible for transport of an extensive range of monocarboxylates including lactate, acetoacetate, pyruvate, and β-hydroxybutyrate, all transported in their anionic form [43, 44]. The affinity for lactate of MCTs varies, with MCT1 having an intermediate-affinity (Km ≈ 3.5 mM) and facilitating both import and export of lactate in a physiological setting, while the high-affinity MCT2 (Km ≈ 0.7 mM) and the low-affinity MCT4 (Km ≈ 28 mM) are more suited to lactate uptake or release, respectively [45]. The functional features of MCT1 include recognition of aliphatic short-chain (carbon chain length two to five) monocarboxylates as substrates, and the Km value for transport decreases with increasing chain lengths of various monocarboxylates. Monocarboxylates with longer-branched

aliphatic or aromatic side chains have also been found to bind to the transporter, but these are not easily released following translocation and may act as potent inhibitors. The classical inhibitor of metabolic transporters, α-cyano-4-hydroxycinnamate, is an example of this type of antagonist [46]. Monocarboxylates that are substituted in the C-2 and C-3 positions with halides, hydroxyl, and carbonyl groups constitute important substrates. The C-2 substitution is preferred over C-3, with the carbonyl group being especially favored, and this allows the carrier to transport a range of naturally occurring monocarboxylates such as pyruvate, lactate, acetoacetate, and β-hydroxybutyrate [47]. Lactate transport through MCTs has been found to be stereospecific with higher affinity for L-lactate when compared to D-lactate [48]. These kinetic properties of MCTs impact their function in vivo and may allow manipulation of specific metabolic pathways in the future.

Connexins and Pannexins

Connexins and pannexins both form hexameric transmembrane pores that are permeable to ions, metabolites, and second messengers (Fig. 1) [49]. There are numerous different isoforms for both connexins and pannexins, and many have cellular and tissue specificity. In the PNS, the major connexins are connexin 32 (Cx32) and Cx26. Pannexin 1 (Panx1) is the primary pannexin expressed in the PNS. Connexins have the capacity to form both gap junctions, which connect one cell directly with another, and hemichannels, which allow for a pore through the plasma membrane, while pannexins form only hemichannels. The exact cargo carried by different connexins and pannexins and the processes used for modulating this transport are not fully defined. One of the better-studied connexins in the PNS, Cx32, is known to transport ATP and is suspected to transport K^+ ions and lactate. In cell cultures, Cx32 is also necessary for the release of ATP, which stimulates the spread of intracellular Ca^{++} waves [50]; in vivo, electrical stimulation of peripheral nerves causes the release of ATP, which is blocked by connexin/gap junction inhibitors [51]. As discussed below in greater detail, disruption of Cx32 leads to the development of x-linked Charcot-Marie-Tooth disease, which is the second most common cause of inherited peripheral neuropathy [52–54]. Pannexins have primarily been investigated for their capacity to transport ATP. Though a metabolic molecule, ATP-transported through plasma membranes has been shown to primarily play a messenger role by binding to pyridine receptors and stimulating Ca^{++} and second messenger systems [55]. Though there are three pannexins [56], Panx1 is the best characterized and has been shown to mediate ATP release and other regulated functions [57–60]. Release of ATP through Panx1 in the PNS appears to contribute to neuropathic pain signals in a mechanism that likely involves microglia and macrophages [61], and may also contribute to Wallerian degeneration [62, 63]. Whether pannexins or ATP also contribute to metabolic support is not yet clear.

Where Are the Metabolic Transporters Located?

The PNS is composed of a number of different cell types that all interact to maintain the major function of the PNS, which is communication to and from the CNS. The major cellular components are the primary neurons (i.e., motor neurons and DRG neurons), which send axons through the peripheral nerves, glial cells (i.e., SCs and satellite glial cells [SGC]), which support and/or myelinate these neurons and axons, and cells important for maintaining the blood nerve barrier (i.e., perineurial glial cells and endoneurial endothelial cells). Each of these cell types have distinct expression patterns for metabolic transporters, which is detailed below and summarized in Figs. 2 and 3.

Motor Neurons

Motor neurons, or more specifically spinal motor neurons, are the efferent neurons of the PNS connecting the CNS with muscles. They include two components: the general somatic efferents and general visceral efferents. The general somatic efferents are comprised of the motor neurons that innervate striated voluntary skeletal muscle. These neurons project their axons through all of the spinal nerves and most of the cranial nerves except I, II, and VIII. General visceral efferents innervate smooth muscle, cardiac muscle, and glands. Proper functioning of these neurons is dependent on continual energy supply, which is primarily glucose during normal physiologic activity. In order to get access to motor neurons, metabolic substrates, including both glucose and monocarboxylates, need to traverse the blood–brain barrier [64]. Glucose is transported through GLUTs, as discussed previously. Among the 14 GLUT family members, GLUT3 is believed to be the primary motor neuron GLUT (Fig. 2) and is located in the neuropil [65, 66], while GLUT4 and GLUT8 are expressed at lower levels in the somata [67–69]. The expression level of GLUTs increases postnatally in the brain [70], which suggests a greater role for GLUTs, or greater dependence on glucose, in the adult as compared to younger brains [67]. Alternatively, the expression of other GLUTs, not yet studied, may contribute to glucose transport during development. A functional role of GLUTs in motor neurons has been suggested by radioactive tracing studies that have correlated treatments that cause motor neuron death, such as nerve injury in neonates, with reduced glucose uptake in the ventral horn of spinal cord [71]. Connexins have also

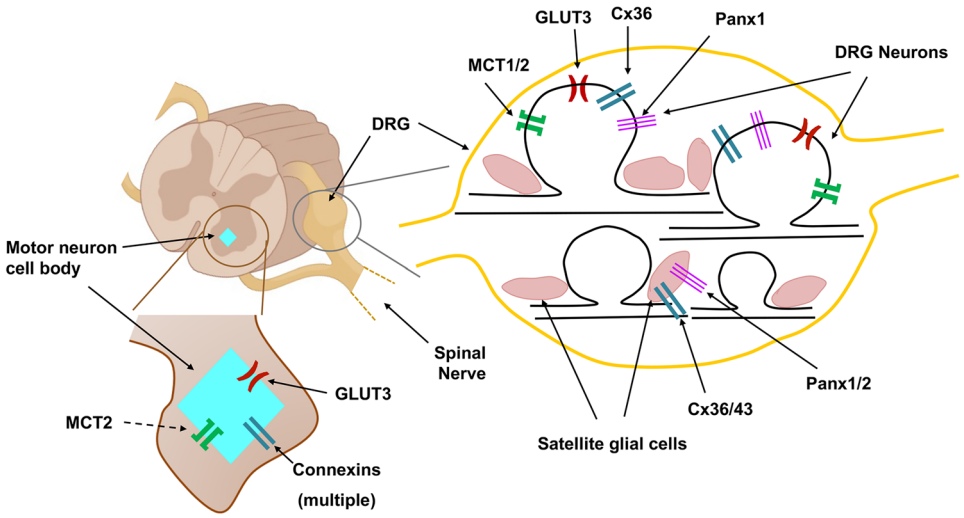

Fig. 2 Localization of metabolic transporters in the peripheral nervous system (PNS) in or adjacent to the spinal cord. Schematic showing the localization of the neuronal cell bodies of the PNS, including the motor neurons and the dorsal root ganglia (DRG) neurons, along with the satellite glial cells (SGC) that support DRG neurons. The localization of metabolic transporters on motor neurons or DRG is also indicated, including specific glucose transporters (GLUT), monocarboxylate transporters (MCT), connexins (Cx), or pannexins (Panx). If localization is presumed, but not proven, the transporter is indicated by a dashed line

been investigated in motor neurons, particularly their role in coordinating synchronous motor neuron firing. Motor neurons from neonatal rats express connexins, including Cx36, Cx37, Cx40, Cx43, and Cx45, as determined by in situ hybridization and immunohistochemistry [72], though this expression appears to be dependent on the state of development since a recent publication has suggested that only Cx36 is truly expressed in motor neurons from early post-natal mice [73]. Both publications focused on their formation of gap junctions, and it remains unclear whether connexins on motor neurons form hemichannels that can transport ATP. In contrast to the experiments investigating GLUTs and connexins, there have been no comprehensive studies of MCTs in motor neurons. Though presumed to express MCT2 like other CNS neurons [74], this has not yet been confirmed in publications.

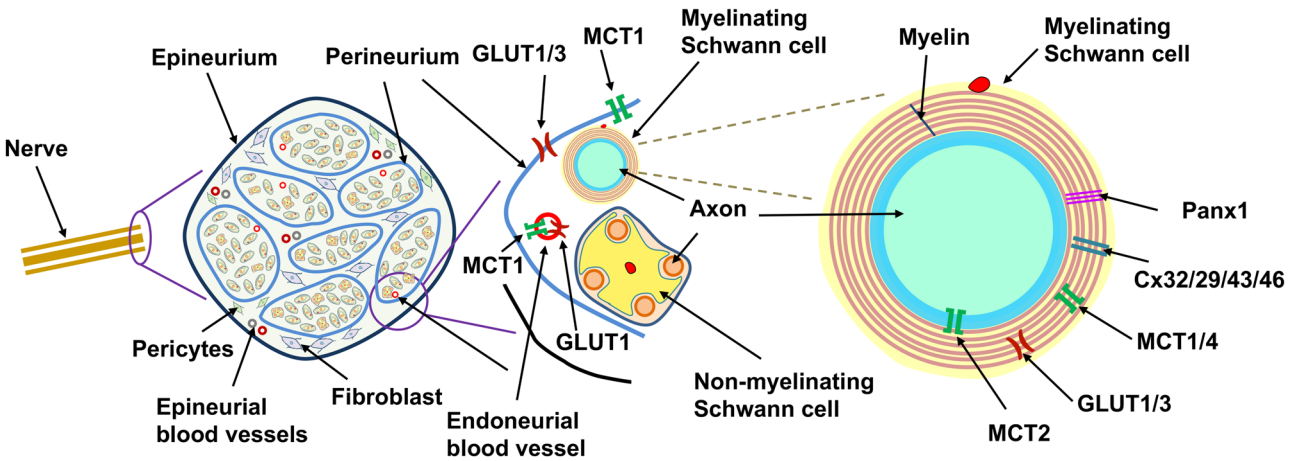

Fig. 3 Localization of metabolic transporters in the peripheral nerve. Schematic showing a cross section of the peripheral nerve, demonstrating the epineurium, which is a fibrous structure that provides support to the nerve, fibroblasts, the nerve fascicles each surrounded by the perineurium, and the components of the endoneurium—axons, myelinating SCs, non-myelinating SCs, and endoneurial blood vessels. Please note the organization of unmyelinated axons into Remak bundles, which are a collection of axons within the basal lamina of a single SC. The localization of specific glucose transporters (GLUT), monocarboxylate transporters (MCT), connexins (Cx), and pannexins (Panx) are indicated on the schematic

Dorsal Root Ganglia Neurons

DRG neurons reside outside of the CNS in ganglia attached to the dorsal roots of spinal nerves. Like the rest of the peripheral nerve, metabolic substrates must first pass through the blood nerve barrier, though it is distinctively more leaky surrounding the DRG [10]. DRG neuronal cell bodies are engulfed by SGCs, which limit the interaction between cell bodies (Fig. 2). DRG neurons are bipolar neurons that carry the sensory neuronal signals from receptors, such as thermoreceptors, nociceptors, proprioceptors, and chemoreceptors, into the CNS. The best studied metabolic transporters in DRG neurons are the pannexins, specifically Panx1 and Panx2. Panx1 expression was increased following nerve injury in almost all DRG neurons, and both Panx1 and Panx2 were increased in SGC [75]. These transporters modulate intercellular communication between DRG somata and SGCs via ATP release and purinergic receptors. In fact, blocking the Panx1 channel in DRG neurons by carbenoxolone reduces tactile allodynia and mechanical hyperalgesia induced by nerve injury, suggesting that neuropathic pain may be partly dependent on Panx1 expression in sensory neurons [60]. Carbenexolone is not, however, specific to Panx1 and blocks all hemichannels and gap junctions, including Cx36, which is also expressed in DRG neurons [76]. These results could therefore be due to disruption of connexin gap junctions and do not specifically confirm a role for Panx1. DRG neurons have also been shown to express MCT1 mRNA, though cellular localization of this transporter by immunohistochemistry has not yet been published [4, 5]. MCT1 may be essential for axon maintenance, since downregulation in DRG neurons cocultured with SCs led to reduced expression of neurofilament, which is an axonal cytoskeletal protein. MCT2 mRNA is also expressed in DRG neurons [4]. GLUTs have also not been thoroughly examined in DRG neurons, though a study in frogs suggests they express GLUT3, but not GLUT1 [77], and these metabolic transporters appear to be altered following peripheral nerve injury [78].

Schwann Cells

SCs, the major glial cells in the PNS, have vital roles in the maintenance and regulation of the PNS by secreting neurotrophic factors, producing extracellular matrix, and accelerating axonal conduction by myelinating axons [79]. Immature SCs originate from neural crest cells and differentiate into two distinct mature SC populations, myelinating and non-myelinating SCs, which envelope large-diameter and small-diameter axons, respectively (Fig. 3). SCs play a key role in axonal myelination of the PNS and facilitate saltatory conduction. The myelin sheath is composed of both compact and non-compact myelin regions. Non-compact myelin borders the nodes of Ranvier, termed the paranode, and is also present in Schmidt-Lanterman incisures. In addition to myelinating axons, SCs also associate with unmyelinated axons in the PNS (i.e., C-fibers), including both nonpeptidergic (for mechanical sensitivity) and peptidergic (for heat/cold sensitivity) axons [80]. Though there is no myelin, SC basal lamina surrounds clusters of unmyelinated axons forming Remak fiber bundles within peripheral nerves [81, 82]. Remak bundles are only seen by electron microscopy, and thus localization of metabolic transporters, which has been primarily accomplished by light microscopy of immunofluorescence or immunohistochemistry, has only been published for myelinating SCs or SC cultures. Similar to oligodendrocytes and astrocytes in the CNS [83, 84], SCs also play a role in providing metabolic support to axons in the PNS [85, 86].

Myelinating SCs express many metabolic transporters, including GLUT1, MCT1, MCT4, Cx32, CX43, Cx46, Cx29, and Panx1 (Fig. 3). As such, they are poised to function as critical cells in the metabolism of the PNS. Rat SCs in vivo [8] and in vitro [87] express GLUT1 around the nodes of Ranvier, the paranodal regions, and Schmidt-Lanterman incisures. Demand for metabolic energy is exceptionally high at or near the nodes of Ranvier, which are unmyelinated regions in the peripheral nerve with high concentration of both Na^+/K^+-ATPase and Na^+-channels that are specialized for electrochemical transmission [8]. In the adjacent paranodal region, where the K^+ channels are concentrated, the myelinated SC surrounds and is adherent to the axolemma, mediated by axoglial junctional complexes, forming the paranodal diffusion barrier. Outside of these regions, the only other region of non-compacted myelin are Schmidt-Lanterman incisures, which are clefts in the myelin allowing solutes and other small molecules to pass through the hydrophobic myelin barrier. The presence of glucose transporters has also been confirmed by 2-deoxyglucose uptake in cultured SCs, and their expression appears to be dependent on axonal membranes [88]. MCT1 and MCT4 are also both expressed in SCs [4, 89, 90]. MCT1 appears to be present in the myelin sheath [91] and Schmidt-Lanterman incisures [4]. The specific localization of MCT4 within SCs is not clear, likely due to its low level of expression, but its expression in SCs is consistent with expression in other cells with high glycolytic activity, such as type 2 skeletal muscle, astrocytes, and white blood cells [4, 92, 93]. Cx32 is localized primarily to non-compact myelin, where the myelin loops are often interconnected by gap junctions composed of Cx32, and disruptions of this gap junction and hemichannel protein leads to X-linked Charcot-Marie-Tooth disease [6, 94, 95]. Dye transfer studies have been used to explore the functional role of Cx32 in SC myelin, pointing to a possible role in myelin metabolite trafficking [96]. Other than Cx32, expression of multiple connexins, i.e., Cx43 [97],

Cx29, and Cx46 (after nerve injury), has been detected in myelin-forming SCs or at different SC developmental stages (neural crest, SC precursor) [98, 99]. Panx1 is also expressed in SCs and primarily functions as a channel for ATP [7]. ATP can be released by both SCs and peripheral neurons and is a component of their intercellular communication [100–102]. The stimulus for ATP release in SCs is glutamate or uridine triphosphate [103], and ATP acts as a critical signaling molecule to modulate peripheral sensitization after sciatic nerve injury [104].

Satellite Glial Cells

The second type of glial cell in the PNS is SGCs. Similar to SCs, SGCs originate from neural crest stem cells [105], but they have unique morphologic features, and localize to ganglia, such as sympathetic ganglia, parasympathetic ganglia, and DRG, where they envelop neuronal cell bodies. SGCs function as homeostatic cells, providing support to sensory neurons [106]. Single-cell transcriptomics demonstrates that SGCs represent a unique cell population, which share molecular markers with both SCs and astrocytes [107]. Increasing evidence suggests that SGCs undergo significant morphological and biochemical changes as a result of peripheral nerve injury or inflammation [108, 109]. They activate PPARα signaling, which are ligand-activated nuclear receptors and key regulators of lipid and carbohydrate metabolism, to promote axon regeneration in adult peripheral nerves [107]. These findings suggest that fatty acid synthase-dependent PPARα activation contributes to axon regeneration. SGCs also respond to diabetic nerve injury by a mechanism that is at least partly mediated by ATP signaling [110].

SGCs express Cx36 and Cx43, as well as Panx1 and Panx2 (Fig. 3) [76, 111]. The connexins have been shown by both dye labeling and patch clamp experiments to form functional gap junctions with other SGCs and also with DRG neurons [112]. The function of these gap junctions in vivo is unclear, but may involve buffering potassium ions in the extracellular space around ganglia neurons by dispersing them through the gap junction-coupled SGCs. Additionally, depolarization of SGCs impact the neuronal firing threshold for adjacent DRG neurons, suggesting possible modulation of sensory nerve activity [112]. Following peripheral nerve injury, SGCs undergo cell division and increase expression of glial fibrillary acidic protein (GFAP) and Cx43 [108]. These alterations in GFAP and Cx43 are also seen following in vitro exposure of SGCs to the chemotherapy, and known neurotoxin, oxaliplatin [113]. Interestingly, media from these oxaliplatin-treated cultures can alter the excitability of DRG neuron cultures, further suggesting that there is cross talk between SGCs and DRG neurons that may be mediated by connexins and pannexins.

Perineurial Glia and Endothelium

The peripheral nerve is protected by a blood-nerve barrier, which allows transport of important metabolites and signaling molecules from the blood, while filtering out many potentially harmful larger molecules and infectious particles. The main cellular components of the blood nerve barrier are perineurial glia, which form the perineurium, and endothelial cells, which form the wall of endoneurial blood vessels [114, 115]. The perineurium bundles axons, SCs, and endoneurium into fascicles and is composed of a multi-cellular sheath made up of flattened, interdigitated perineurial glia [116, 117]. Perineurial glia cells are derived from the CNS, and exit the spinal cord along with the developing peripheral nerve. They respond to nerve injury and are essential mediators of nerve regeneration by phagocytizing debris and forming glial bridges across injury sites [118]. Perineurial glia also function to regulate the transport of energy metabolites into and out of the endoneurium by expressing GLUT1 and MCT1 (Fig. 3) [5, 119–122]. Similar to perineurial glia, endothelial cells in endoneurial blood vessels have tight junctions, which restrict the flow of solutes and express specific metabolic transporters, including GLUT1 and MCT1 [120, 123].

Why Are Specific Metabolic Transporters Important for Physiologic Function and Disease?

The function and integrity of the PNS require uninterrupted energy supply through metabolites, particularly glucose, and lactate. The transfer of metabolic substrates from SCs to axons was reported nearly two decades ago [86], but the specific mechanism and critical metabolites for this transfer remains unclear. Though glucose supplied from the vasculature through GLUTs is likely the major source of energy, new research provides evidence for a prominent role of lactate and other monocarboxylates functioning through MCTs. Described originally in the brain as the astrocyte-neuron lactate shuttle [124–126], lactate and MCTs have now also been shown to play an important role in the PNS [4, 5, 127]. This was shown directly in electrophysiology studies of peripheral nerves ex vivo, in which blocking the metabolism of SC glycogen or transfer of lactate through MCTs led to energy deprivation of axons, which could be reversed by supplying exogenous lactate [128]. Studies in vivo have also shown the importance of energy metabolites and their transporters for maintaining specific functions in the PNS, thus supporting a role for neuron-glia metabolic coupling in the PNS [4, 89, 127].

Maintenance of Myelin Sheath, Neuromuscular Junction Innervation, and Axon Integrity Contribution of SC MCT1 and Lactate Production

MCT1 has recently been investigated in SCs of the PNS and found to contribute to both myelin maintenance and neuromuscular innervation. Using conditional cre-lox null mice, selective ablation of MCT1 within SCs led to impaired maintenance of myelin as measured by tail electrophysiology and histology of the sural nerve in mice 4 months of age or older, potentially through alterations in intracellular energy reducing the production of lipids essential for myelin production [89]. Interestingly, the alteration in myelin only occurred in sensory neurons and these mice did not show any signs of axonal injury or dysfunction, suggesting some redundancy in the metabolic support to axons. Using a different conditional cre-lox mouse to ablate MCT1 from SCs, a separate group of researchers found no abnormalities in myelination of the sciatic nerve at 1 year of age but found significant impairments of neuromuscular innervation and a trend towards reduced numbers of intraepidermal nerve fibers [129]. Transcriptional analysis of laser-captured motor neurons from these mice showed several alterations, including reduced expression of cytoskeletal genes, suggesting that reduced metabolic support of axons may have contributed to distal axon degeneration and denervation of neuromuscular junctions. The reasons for the differences between the studies are not clear. Certainly, there were differences in the techniques for quantifying electrophysiology, which was done biweekly in the first study and only at 1 year of age in the second, and histology, which was evaluated in the sensory sural nerve in the first study and the mixed motor and sensory sciatic nerve in the second. Additionally, the first study did not evaluate neuromuscular junction innervation. Further work will likely need to be completed to fully reconcile these two studies and better define the exact function of MCT1 in SCs. Despite this lack of clarity on its exact function, these studies strongly suggest that MCT1 plays an important role in SC function and metabolic interactions with axons in growth, development, and aging.

The presence of glycogen, which is the primary intracellular metabolic storage molecule, within SCs suggests these cells are an essential source of energy substrates, particularly lactate, for myelinated axons during episodes of increased metabolic activity or relative hypoglycemia [128]. Lactate is produced by glycolytic metabolism of glucose or glycogen within SCs and then is transported into axons via MCTs. Within axons, lactate or other monocarboxylates can be oxidized to pyruvate, which can be further metabolized through the Krebs cycle to produce NAD and ATP [85, 128]. MCT1 is the lactate transporter with the highest level of expression in peripheral nerves, being expressed in SCs along with other cell types [4, 5, 119]. Further evidence for this metabolic link between SCs and axons came from a paper investigating the role of LKB1 in SCs [85]. In this study, the investigators downregulated LKB1 selectively in SCs and found that there was a disruption in SC mitochondrial oxidative metabolism and degeneration of primarily unmyelinated sensory axons in transgenic mice. As compensation for the loss of oxidative metabolism, the mice upregulated glycolytic pathways and had increased lactate production. To demonstrate that lactate production was partially protective, the investigators blocked production of lactate with 2-deoxyglucose and found that there was significantly greater axon loss than in the original LKB1 null mice. Though the specific role of MCTs was not investigated in this study, these transporters were presumably at least partly responsible for the export of lactate out of SCs to support axons. Taken together with the conditional MCT1 null studies, these experiments suggest that MCT1 and lactate in SCs are necessary to support the survival of unmyelinated sensory axons, the maintenance of myelin sheaths on sensory axons, and the innervation of neuromuscular junctions.

Regeneration Following Peripheral Nerve Injury—Role for MCT1 and SC-Derived Lactate

Unlike axons in the central nervous system, PNS axons have the capacity to regenerate following injury. The process of regeneration involves first Wallerian degeneration, where the components of the injured axons are cleared away by SCs and macrophages, and later SC tubes are formed allowing regeneration of axons toward their original targets [130]. If this regeneration occurs quickly and the distance of regeneration is short, peripheral nerve regeneration can lead to almost complete recovery of function in both patients and animal models. If, however, there is a delay in nerve repair or the distance to reinnervate the target is long, the regeneration will be incomplete leading to significant permanent disability [131]. Thus, better understanding the mechanism of regeneration is necessary to potentially accelerate nerve regeneration and improve outcomes in patients with nerve injuries. Very little is known about the role of metabolic transporters in nerve regeneration. As a first approach, MCT1 heterozygous null mice, which have 50% of MCT1 in the PNS, or wild-type mice underwent sciatic nerve crush, which is a classic model to investigate peripheral nerve regeneration [5]. Nerve regeneration, as measured by nerve electrophysiology, histology, and neuromuscular junction reinnervation, was impaired in transgenic mice with reduced expression of MCT1. Given MCT1 is expressed in many cell types in the PNS, as described above, the exact mechanism by which MCT1 contributes to nerve regeneration is not yet clear. Future studies with conditional null mice should help clarify this critical issue.

A recent publication sheds further light on the role of MCTs and the SC in the metabolic support of injured peripheral nerves [132]. In response to sciatic nerve transection, adjacent SCs upregulate glycolytic, but not mitochondrial oxidative, metabolism. To test the importance of this metabolic shift, the investigators knocked down components of the glycolytic pathway in SCs, specifically GLUT1, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3, and lactate dehydrogenase-A, or blocked MCTs to prevent lactate release from SCs and showed more rapid axon degeneration following injury. The authors then went on to show that the glycolytic shift was dependent on the mTOR pathway through downstream mediators of metabolic pathways, Hif1alpha and c-Myc. This paper shows that metabolic support from SCs, acting through MCTs, supports axons and provides enhanced protection against axonal degeneration following injury, and is the most direct evidence, to date, of a specific role for SC MCTs in the metabolic support of injured peripheral nerves.

Diabetic Peripheral Neuropathy—Role of Glucose and Monocarboxylate Transporters

Diabetic peripheral neuropathy (DPN) is one of the most common complications in patients with diabetes and can lead to severe pain, numbness, weakness, and balance issues [133]. The exact cause of DPN is unknown but likely involves both abnormalities in vascular function and cellular metabolism. Given that there are no treatments to prevent or improve DPN, better understanding the pathogenesis of the condition is critical to potentially developing effective therapies in the future. In response to elevated blood sugars and hyperlipidemia seen in diabetes, many metabolic transporters, including GLUT1, GLUT3, and MCT, are altered in patients [134] and mouse models [135], though these transporters are not changed in all tissues or models of the disease [136, 137]. In both patients with diabetes and diabetic mouse models, GLUT1 is reduced in many cell types, including red blood cells, cardiac and skeletal muscle fibers, and perineurium [87, 134]. The mechanism for reduced GLUT1 is not yet clear. Initially presumed to be compensation for elevated serum glucose levels, a recent publication suggests that reduction in GLUT1 is actually downstream from interferon-gamma, which is a pro-inflammatory cytokine [138]. This same publication also found that reduced expression of GLUT1 in SCs impairs the proliferative capacity of SCs, which is a necessary function for nerve repair following injury. Whether this alteration of SCs actually contributes to DPN is unknown, but this is an area that should be further investigated.

MCT1 is another metabolic transporter that appears to be altered in diabetes [134, 135]. In order to better understand the potential contribution of MCT1 to DPN, MCT1 heterozygous null mice, as discussed above, were evaluated in the streptozotocin model of type 1 diabetes [90]. In this model, streptozotocin is injected into mice to induce islet cell injury in the pancreas and reduced insulin production. In mice that developed hyperglycemia, but not mice that did not become hyperglycemic or were treated with insulin to correct hyperglycemia, MCT1 heterozygous null mice developed more severe DPN than wild-type mice. DPN was measured in this study by electrophysiology, behavioral testing, and histology of peripheral nerves. Similar to the study in nerve regeneration, future studies are necessary to better characterize the exact mechanism by which MCT1 contributes to the development of DPN.

GLUT1 Deficiency—an Uncommon Cause of Peripheral Neuropathy

As discussed previously, glucose is regulated from the bloodstream to the nervous system by GLUT1, which is encoded by the gene *SLC2A1*. Mutations in this gene cause glucose transporter deficiency syndrome, due to reduced glucose transport from the blood to the nervous system. Usually inherited as an autosomal dominant hereditary disease, the most common symptoms in patients with this condition are seizures, but reduced glucose supply during development also frequently leads to global developmental delay, microcephaly, motor ataxia, and dystonia [139]. There have been several animal models produced to mimic this syndrome, including constitutive knockouts and siRNA-delivered mice [140], but a recently published conditional null mouse may provide the most accurate model for this disease [141]. In this model, the investigators developed a GLUT1 flox conditional null mouse, and by mating the heterozygotes with endothelial-specific Cre mice, they were able to generate a model with reduced GLUT1 only in endothelial cells. These mice recapitulate many of the findings in patients, with the mice developing seizures and microcephaly, and confirm that dysfunction in these vascular cells is the primary source for the severe CNS manifestations of the disease. Though not commonly reported, a relatively recent report found peripheral neuropathy in 2 of 10 individuals from a Norwegian pedigree with a c.823G > A (p.Ala275Thr) *SLC2A1* mutation [142]. There was little characterization of the peripheral neuropathy in this publication and no discussion of possible comorbid conditions that could have contributed to peripheral neuropathy, but the report is intriguing and suggests that the PNS may also be vulnerable to reduced glucose supply. Further investigation of patient or the mouse model will be necessary to clarify this issue and determine the mechanism for nerve degeneration.

X-Linked Charcot-Marie-Tooth—Genetic Mutations in Cx32 Lead Directly to Peripheral Nerve Injury

X-Linked Charcot-Marie-Tooth (CMT-X), which is caused by mutations in the Cx32 gene, *GJB1*, is the second most common form of inherited peripheral neuropathy [95]. The symptoms of CMT-X include weakness, muscle atrophy, numbness, and foot deformities [143]. Electrophysiologic and histologic studies have shown that CMT-X patients have both axonal loss and myelin sheath degradation, which distinguishes this disease from other common inherited neuropathies, such as CMT1A and CMT2A, which affect only the myelin sheath or axon, respectively [144]. Most, but not all, of the *GJB1* mutations that cause CMT-X lead to reduced or absent function of Cx32 channels, and the severity of neuropathy appears to correlate with the degree of Cx32 disruption (i.e., lack of ion transport or expression on plasma membrane) [145]. In addition, Cx32-null mice develop peripheral neuropathy and replicate many of the features of the human disease [146], and overexpression of Cx32 specifically in SCs prevents or reverses the peripheral nerve injury in null mice [147, 148]. Thus, it is generally believed that CMT-X occurs by loss of a critical function or functions of the Cx32 protein. Despite knowing the genetic mutations that cause the disease, the mechanism for peripheral nerve injury in CMT-X remains unknown. As discussed previously, Cx32 is known to form both gap junctions and hemichannels in SCs, being localized to the Schmidt-Lanterman incisures and paranodal loop regions of the myelin [6, 94]. These channels allow the passage of many small molecules and solutes, including Ca^{++}, K^+, cAMP, and IP_3 [94]. However, they also allow transport of ATP and lactate through the hydrophobic myelin sheaths [51, 149], which could be important for energy support to axons, particularly the internodal regions, which are covered by myelin. Though there is still much to learn about the physiologic role of Cx32 in peripheral nerves, the consensus that reduced Cx32 function contributes to the disease has opened the door to potential genetic treatments for patients.

Manipulating Metabolism as Potential Therapeutics for PNS Diseases

There have been many advances in gene therapy for the treatment of medical disease, as a whole, and these have recently begun to be utilized for neurologic diseases, as well. The most prominent success has come in the treatment of spinal muscular atrophy [150], but there are also late stage clinical trials for Duchenne's muscular dystrophy [151], amyotrophic lateral sclerosis [152], and Huntington's disease [153]. These success stories have ramifications for inherited peripheral nerve diseases, such as CMT-X. Since loss-of-function mutations of *GJB1* most commonly cause CMT-X, gene replacement therapy may be a viable treatment option in the near future. Such an approach has been used successfully in mouse models, where intraneural gene delivery using a lentiviral vector [154] or intrathecal gene delivery with AAV9 [148] led to increased *GJB1* expression in SCs, amelioration of nerve pathology, and improved motor function in the *GJB1* knockout mouse. These studies suggest that targeting specific genes within the PNS, particularly in SCs, may be clinically feasible and opens up the possibility of treating neurologic diseases with defects in intracellular metabolism.

A second approach to target metabolism for the treatment of peripheral nerve diseases has focused on delaying or preventing axon degeneration. Peripheral nerve injury models have shown that degeneration of axons involves an intracellular signaling cascade in injured axons that ultimately leads to the depletion of the bioenergetic cofactor NAD^+, leading to energetic collapse and structural degeneration of axons. Elevated levels of NAD^+ or ATP concentrations in injured axons confer axon protection. These properties have been used to develop new potential therapeutics for peripheral nerve diseases, involving SARM1 inhibitors that protect axons from degeneration by reducing the breakdown of NAD^+ [155]. In addition to manipulating intrinsic axonal processes, SCs form a connection with the axons and support dynamic responses shortly after axonal injury, long before axonal disintegration occurs [132]. Thus, manipulation of SCs may be capable of supporting axons and preventing or delaying degeneration. Though the first treatments will most certainly target specific SC genetic abnormalities, such as in CMT-X or inherited demyelinating peripheral neuropathies, future therapies may more generally upregulate specific metabolic function in SCs to more globally support and protect axon functions and survival.

Final Thoughts

The disruption of energy support to the peripheral nerve leads to dysfunction or degeneration of both axons and supporting cells. For this reason, cells have developed critical, and often redundant, pathways for maintaining energy supply through the expression of metabolic transporters. In the PNS, energy metabolites, including glucose and monocarboxylates such as lactate, are transported through the specialized endothelium in endoneurial blood vessels or perineurial glial cells via specific transporters. Once within the endoneurium, these metabolites are taken up into neurons where they can be further metabolized to provide fuel for the cell, primarily in the form of ATP. The exact contribution of different metabolic transporters to cellular biology within the peripheral nerve is starting to be elucidated, primarily by cell-specific transporter null mice, but further experiments are still necessary. Several factors have made the study of

metabolism difficult in the nervous system, in general, and peripheral nerves specifically. First, most transporters and channels are bidirectional, and thus cellular localization is often not enough to presume whether metabolites are being imported or exported from a given cell. Second, the importance of maintaining a continuous supply of energy has necessitated the presence of redundant, backup systems that can be utilized when one transporter is pathologically, or experimentally, reduced. Third, all of these transporters are membrane-bound and many are embedded in the myelin of nerves, which makes localization and quantification difficult by immunohistochemistry and western blots, respectively. Despite these challenges, progress is now being made that will hopefully better define the function and regulation of these critical transporters and their respective metabolites.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-021-01150-2.

Funding This review was funded by the National Institute of Neurological Disorders and Stroke (R01NS099320-01) to Dr. Brett Morrison.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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