● **INVITED REVIEW**

Metabolic pathways as possible therapeutic targets for progressive multiple sclerosis

Rebecca M. Heidker[1], Mitchell R. Emerson[2], Steven M. LeVine[1, *]
1 Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS, USA
2 Department of Pharmaceutical Sciences, College of Pharmacy-Glendale, Midwestern University, Glendale, AZ, USA

Abstract
Unlike relapsing remitting multiple sclerosis, there are very few therapeutic options for patients with progressive forms of multiple sclerosis. While immune mechanisms are key participants in the pathogenesis of relapsing remitting multiple sclerosis, the mechanisms underlying the development of progressive multiple sclerosis are less well understood. Putative mechanisms behind progressive multiple sclerosis have been put forth: insufficient energy production *via* mitochondrial dysfunction, activated microglia, iron accumulation, oxidative stress, activated astrocytes, Wallerian degeneration, apoptosis, *etc*. Furthermore, repair processes such as remyelination are incomplete. Experimental therapies that strive to improve metabolism within neurons and glia, *e.g.*, oligodendrocytes, could act to counter inadequate energy supplies and/or support remyelination. Most experimental approaches have been examined as standalone interventions; however, it is apparent that the biochemical steps being targeted are part of larger pathways, which are further intertwined with other metabolic pathways. Thus, the potential benefits of a tested intervention, or of an established therapy, *e.g.*, ocrelizumab, could be undermined by constraints on upstream and/or downstream steps. If correct, then this argues for a more comprehensive, multifaceted approach to therapy. Here we review experimental approaches to support neuronal and glial metabolism, and/or promote remyelination, which may have potential to lessen or delay progressive multiple sclerosis.

Key Words: *acetyl-coenzyme A carboxylase; biotin; estrogen; iron; Kynurenine pathway; mitochondria; thyroid hormone; remyelination; stem cells; vitamin D*

Introduction
Disease modifying therapies act by disrupting various facets of the immune response to ameliorate disease activity in patients with relapsing remitting multiple sclerosis (RRMS). These therapies can slow the development of disability and as a corollary, they may possibly diminish the conversion of RRMS to secondary progressive multiple sclerosis (SPMS) (Trojano et al., 2007, 2009; Gold et al., 2010; Kappos et al., 2015; Giovannoni et al., 2016; Wingerchuk and Weinshenker, 2016). However, once a patient develops SPMS, or if a patient has primary progressive multiple sclerosis (PPMS), then immunotherapies are generally not effective in lessening the disease course (Wiendl and Hohlfeld, 2009; Wingerchuk and Weinshenker, 2016; Sartori et al., 2017). Two exceptions are ocrelizumab, an anti-CD20 antibody that depletes B cells, and siponimod, a modulator of the sphingosine 1-phosphate receptor. Ocrelizumab, which is approved for use in PPMS patients, lessens the probability of disease progression (Montalban et al., 2017) while siponimod has been shown to reduce the risk of disability progression in SPMS patients (Kappos et al., 2016; Mao-Draayer et al., 2017). However, disease progression still occurs in most PPMS or SPMS patients treated with these medications, and when viewed in combination with negative results from other immunotherapies, it suggests that there are additional mechanisms outside of the immune system that play a role in advancing multiple sclerosis (MS) pathology. Although we do not have a complete understanding of the pathogenesis of the progressive forms of this disease, putative mechanisms have been put forth. It has been proposed that inflammatory demyelination eventually leads to neurodegeneration by various mechanisms including, but not limited to, energy depletion through mitochondrial dysfunction and/or hypoxia related processes, oxidative stress, activated microglia, activated astrocytes, Wallerian degeneration, iron accumulation, and apoptosis (Weigel et al., 2014; Mahad et al., 2015; Kawachi and Lassmann, 2017). While these mechanisms are associated with progressive MS, they likely begin during RRMS prior to the full conversion to SPMS. Interventions that act on one or more of these proposed mechanisms, or that assist in the repair of the central nervous system (CNS), are worth exploring for their potential as a treatment, or adjunct therapy, for patients with progressive MS. This paper will focus on a subset of these potential interventions, particularly those that facilitate metabolism to support neuronal and oligodendrocyte functions, and that possibly promote remyelination efforts (**Table 1**).

The Intertwined Roles of Biotin, Iron and Vitamin D for Metabolic Support
Adenosine triphosphate (ATP) is necessary in the CNS for maintenance of membrane potentials, synaptic activities, metabolic functions of neuronal and glial cells, etc. Maintenance of membrane potentials by Na^+/K^+ ATPases in healthy neurons accounts for a substantial portion of a neuron's

energy consumption (Howarth et al., 2012), which can be altered by inflammation and demyelination (Trapp and Stys, 2009). This can cause a disparity of energy production versus expenditure known as "virtual hypoxia" that could lead to events that result in axonal degeneration and neuronal dysfunction or degeneration (Stys, 2004; Trapp and Stys, 2009; Sedel et al., 2016; Kawachi and Lassmann, 2017).

Recently, an early study indicated that high dose biotin therapy (HDBT) improved results for the expanded disability status scale and/or the timed 25-foot walk in 12.6% of patients with progressive MS (Tourbah et al., 2016), but these positive results require additional verification (Chataway, 2016). The putative mechanisms of action that were proposed for HDBT focused on metabolic support, *i.e.*, promoting remyelination by enhancing fatty acid synthesis *via* increasing the functionality of biotin containing carboxylases and facilitating energy production in neurons, potentially countering virtual hypoxia (Sedel et al., 2016). Other mechanisms, *e.g.*, regulation of gene expression or limiting immune responses, may also be involved (Heidker et al., 2016; Sedel et al., 2016) (**Table 1**).

Upon examination of the metabolic pathways that involve biotin, it is apparent that other nutrients such as iron are utilized by these pathways. For example, both biotin and iron participate in biochemical reactions involved in energy production (Heidker et al., 2016). Multiple biotin-containing enzymes are involved with the generation of intermediates of the tricarboxylic acid (TCA) cycle that supply the electron transport chain (ETC), which utilizes iron containing enzymes (*e.g.*, iron-sulfur clusters, cytochrome C which contains heme) for the further production of ATP. Heme synthesis is an additional interrelationship, requiring iron as well as metabolites generated by the biotin-dependent pyruvate and methylcrotonyl carboxylases (Atamna, 2004; Atamna et al., 2007; Voet and Voet, 2011).

Lipid synthesis is another example of intertwined roles for biotin and iron. The biotin-dependent acetyl-coenzyme A carboxylase 1 initiates lipid synthesis, which requires heme and iron-sulfur clusters as cofactors for several enzymes, as does cholesterol synthesis (Voet and Voet, 2011). As lipids and cholesterol are key components of myelin, increased synthesis of these compounds in conjunction with remyelination has been proposed as a therapeutic mechanism of HDBT (Sedel et al., 2016). Interestingly, this hypothesis is somewhat in contrast with the usage of simvastatin, which inhibits cholesterol synthesis, to treat SPMS. Simvastatin was shown in a phase II clinical trial to potentially have value for treating SPMS, with the putative therapeutic mechanisms including immunomodulative, neuroprotective or vascular effects (Chataway et al., 2014). However, simvastatin can hinder myelination during development (Xiang and Reeves, 2009) and potentially impair remyelination efforts (Miron et al., 2009), which in theory could limit its usefulness as a treatment for progressive MS.

While HDBT likely supports metabolism, it may be acting to correct a biotin deficiency that is present in a subgroup of MS patients that developed consequentially to have a prolonged chronic disease or that occurred independent of MS (Heidker et al., 2016; Siddiqui et al., 2017). In addition, the prolonged inflammation associated with MS could, in theory, cause a reduction in the availability of iron for biochemical pathways in neurons and oligodendrocytes (Heidker

et al., 2016). Thus, a localized deficiency of iron (or heme) at the biochemical level, but not necessarily at the tissue or systemic level, would act to lessen support for energy production, remyelination and/or the maintenance of myelin (Heidker et al., 2016). Interestingly, in patients with chronic progressive MS, normally appearing white matter areas have reduced levels of iron together with low levels of inflammation (Hametner et al., 2013). Additionally, anemia has been identified as a comorbidity in MS, and it may aggravate disease, *e.g.*, increasing the risk of a relapse (Tettey et al., 2016). However, supplying neurons and oligodendrocytes with optimal iron levels could be complicated because iron is present in excess in some brain regions (*e.g.*, thalamus, caudate, globus pallidus, putamen) and it can become deposited around damaged vessels in patients with MS, *e.g.*, due to microhemorrhaging (Weigel et al., 2014). In theory, this excess iron could promote pathology by catalyzing oxidative or nitrative tissue damage, increasing proinflammatory cytokine production, supporting increased glutamate release potentially leading to excitotoxicity, *etc*. (Weigel et al., 2014). Microinjection of ferritin, which can bind copious amounts of iron, into the rat spinal cord resulted in oligodendrocyte and neuronal toxicity, but the injected ferritin also stimulated the proliferation of progenitor cells that differentiated into oligodendrocytes (Schonberg et al., 2012). Thus, identifying a means to achieve an appropriate level of iron for optimal support of metabolism and remyelination efforts while limiting the effects of excess iron contributing to pathogenesis would be a desired goal as part of an intervention strategy.

Interestingly, vitamin D has been shown to lessen iron induced toxicity in the locus coeruleus and cultured neuroblastoma cells (Chen et al., 2003; Uberti et al., 2016), suggesting that vitamin D could help protect against iron related damage in MS. Low levels of vitamin D have also been correlated with an increased risk of developing MS, and levels may be inversely associated with progression of disease activity in RRMS patients (Ascherio and Munger, 2016; Hempel et al., 2017). Iron, as part of heme, is necessary for the metabolism of vitamin D (Toxqui and Vaquero, 2015), and as stated above, products of the biotin-containing enzymes, pyruvate carboxylase and methylcrotonyl carboxylase, are used in the synthesis of heme. Vitamin D plays a role in myelination and remyelination by increasing differentiation of oligodendrocyte precursor cells (OPCs), presumably *via* activation of the vitamin D receptor and its heterodimer partner, the retinoid X receptor gamma (de la Fuente et al., 2015). Additionally, vitamin D increased the expression of oligodendrocyte/myelin proteins (*i.e.*, myelin oligodendrocyte glycoprotein and CNPase) when administered during remyelination following demyelination induced by cuprizone (Mashayekhi and Salehi, 2016). These effects likely occur in conjunction with vitamin D's immunomodulatory role (Dankers et al., 2017). Vitamin D supplementation has been tested in various clinical trials that focused mostly on RRMS or clinically isolated syndrome, but should also be thoroughly evaluated in patients with progressive MS (Pozuelo-Moyano et al., 2013), especially given its putative action on remyelination and possible ability to lessen iron mediated CNS damage.

Vitamin D, biotin and iron may all work together to sup-

Table 1 Potential approaches to support metabolism and/or remyelination for progressive multiple sclerosis

Approach	Possible beneficial impact	References
High dose biotin therapy	Support metabolism; promote remyelination; regulate gene expression; immunomodulation	Heidker et al., 2016; Sedel et al., 2016
Iron	Support metabolism; promote remyelination	Stephenson et al., 2014; Heidker et al., 2016
Vitamin D	Support remyelination; immunomodulation; lessen iron-mediated damage	Chen et al., 2003; de la Fuente et al., 2015; Mashayekhi and Salehi, 2016; Uberti et al., 2016; Dankers et al., 2017
Ketogenic diet	Support metabolism; increase antioxidants; lessen production of reactive oxygen species	DeVivo et al., 1978; Kim et al., 2012; Storoni and Plant, 2015
Modulate kynurenine pathway	Support metabolism; reduce excitotoxicity	Vorwerk et al., 1996; Lovelace et al., 2016; Lim et al., 2017
Thyroid hormone	Metabolic regulation; support remyelination	Bernal, 2015; Zhang et al., 2016
Estrogen	Support remyelination; lessen inflammation	Zhang et al., 2004; Okada et al., 2008, 2010; Deckx et al., 2013; Khalaj et al., 2013; Khan and Ansar Ahmed, 2016
Stem cells	Support remyelination; support metabolism; support growth and regeneration; neuroprotective; replace central nervous system cells; immunomodulation	Jadasz et al., 2012; Teixeira et al., 2013; Markham et al., 2014; Meamar et al., 2016

port myelination and facilitate remyelination efforts (**Table 1**). Maintaining optimal levels of these nutrients is predicted to enable the best outcome for patients with progressive MS since a deficiency in one could affect or undermine the functions of the others.

Additional Experimental Approaches to Promote Metabolism

Heightened ATP consumption is thought to occur following demyelination due to the redistribution of channels along the axon to support the propagation of impulses (Hollingsworth et al., 2017). This is contrasted with healthy myelin which helps maintain the distribution of sodium channels necessary for saltatory conduction thereby resulting in efficient energy utilization, while oligodendrocytes also provide trophic support for axons (Hollingsworth et al., 2017). The repair process of remyelination depends on the migration and differentiation of OPCs into oligodendrocytes capable of forming myelin, but remyelination is an incomplete and heterogenous process (Hollingsworth et al., 2017). As in myelination, proper metabolic support should facilitate remyelination efforts while also supporting axonal processes and other neuronal functions (Heidker et al., 2016). Along these lines, additional therapies that support ATP production and/or drive remyelination in the CNS are being explored, *e.g.*, ketogenic diet, thyroid hormone, estrogen, and stem cells (SCs) (**Table 1**). While many of these studies have been performed in the context of RRMS, or related models, they may provide important insight into therapeutic mechanisms that may help ameliorate progressive forms of MS.

Mitochondria generate ATP within neurons *via* oxidative metabolism (Bélanger et al., 2011), with decreased mitochondrial functionality contributing to neurodegeneration (Storoni and Plant, 2015). Glucose which is metabolized into pyruvate *via* glycolysis, supports ATP generation *via* the oxidative pathways of the TCA cycle and the ETC (Voet and Voet, 2011; Mathur et al., 2014). Disturbances of glucose and pyruvate metabolism in MS patients are indicated by elevated blood or cerebrospinal fluid levels of pyruvate, alpha-ketoglutarate, and citrate, while SPMS patients exhibit

increased CSF levels of metabolites from both extra-mitochondrial glucose and anaerobic metabolism (Mathur et al., 2014). A ketogenic diet, which can increase ATP levels, has been proposed as a possible supportive treatment for progressive MS (Storoni and Plant, 2015). In rats, a ketogenic diet produced higher ATP/adenosine diphosphate ratios in the cerebrum than normal diets, making it conceivable that a ketogenic diet might assist in providing more adequate levels of ATP for neuronal support (DeVivo et al., 1978). Additionally, ketogenic diets may increase antioxidants and promote the expression of uncoupling proteins, which may lessen the production of reactive oxygen species (ROS) (Storoni and Plant, 2015). When tested in murine experimental autoimmune encephalomyelitis (EAE), a model of MS, a ketogenic diet caused decreased levels of ROS and inflammatory cytokines (Kim et al., 2012).

Rats exposed to a ketogenic diet for 3 weeks had an increased production of kynurenic acid (KA) in certain areas of the brain (Żarnowski et al., 2012). Systemic administration of L-kynurenine, a precursor of KA, has been shown to have neuroprotective properties, *i.e.*, reducing N-methyl-D-aspartic acid induced death of retinal ganglion cells in rats (Vorwerk et al., 1996). KA, which can block excitotoxicity, is generated by the kynurenine pathway (KP), through the degradation of the amino acid tryptophan (Lovelace et al., 2016; Lim et al., 2017). This process also results in the production of nicotinamide adenine dinucleotide (NAD^+), which is involved in multiple processes, *e.g.*, transcription, signaling and cellular metabolism including glycolysis, TCA, and beta oxidation (Cantó et al., 2015; Lovelace et al., 2016; Lim et al., 2017). Chronic inflammation, such as that found in conditions like MS, can cause the KP to become activated and dysregulated (Lovelace et al., 2016; Lim et al., 2017). This dysregulation leads to lower NAD^+ levels and the possible depletion of energy (Lovelace et al., 2016; Lim et al., 2017). Paradoxically, two other metabolites of the KP, 3-hydroxykynurenine and quinolinic acid (QA), are both excitotoxins and are elevated in the spinal cord of EAE rats (Chiarugi et al., 2001; Lovelace et al., 2016). Excessive QA with insufficient KA leads to excitotoxicity, and a recent study has shown the ratio of QA to KA is elevated in progressive forms of MS, but not RRMS, making it a potential biomarker of

disease progression (Lim et al., 2017). Together, these factors make regulation of the KP an attractive therapeutic target for progressive MS (Lim et al., 2017).

Hormones, such as TH which is well known for its role in metabolic regulation, may play a supportive role in remyelination. As developmental myelination is driven in part by TH stimulating differentiation of OPCs (Bernal, 2015), researchers have begun exploring the possibility that TH may increase remyelination in MS. Positive results, including lessening impulse propagation deficits, decreasing myelin loss, and lowering axonal degeneration were seen in rats with EAE that were treated with TH starting at the presentation of clinical signs, *i.e.*, 10 days post immunization (Dell'Acqua et al., 2012). Similarly, injections of TH after cuprizone administration in murine models, led to increased differentiation of OPCs and enhanced remyelination (Zhang et al., 2016). These effects may be mediated by increased transcription of Kruppel-like factor 9 (KLF9), which encourages differentiation of OPCs (Zhang et al., 2016). The positive results in animal studies have led to a phase I clinical trial (NCT02760056) which is underway to investigate the dosage and safety of Liothyronine (T3) in patients with MS.

Estrogen, which regulates reproduction, energy balance, and immune function (López and Tena-Sempere, 2015; Khan and Ansar Ahmed, 2016), is also being considered as a therapeutic approach for MS. Remission rates of RRMS approach nearly 80% during the later stages of pregnancy when estrogen is elevated (Vukusic et al., 2004; Gold and Voskuhl, 2009; Deckx et al., 2013). A phase II trial comparing women treated with either estriol (a form of estrogen secreted by the placenta during pregnancy) or a placebo, each in combination with glatiramer acetate, showed decreased relapse rates of MS with estriol treatment as compared to placebo (Voskuhl et al., 2016). It is thought that activation of estrogen receptors decreases the expression of inflammatory signaling molecules, thereby diminishing inflammation and the associated demyelination seen in MS (Deckx et al., 2013; Khan and Ansar Ahmed, 2016). Estrogen also appears to support the proliferation, differentiation, and process formation of oligodendrocytes (Zhang et al., 2004; Okada et al., 2008, 2010; Khalaj et al., 2013), possibly promoting remyelination. In addition to estrogen, a selective estrogen receptor modulator, Tamoxifen, has recently been shown to increase rates of remyelination both *in vitro* and in rats following focal demyelination induced by ethidium bromide (Gonzalez et al., 2016). The efficacy of estrogen receptor agonists is being explored using mouse models (Kumar et al., 2013; Moore et al., 2014; Itoh et al., 2017).

Another area of active research has been exploring the use of SCs as a possible treatment for MS. Autologous hematopoietic SCs have been used in the regeneration of the immune system following immunoablation with some success in MS patients with aggressive disease (Mancardi and Saccardi, 2008; Muraro et al., 2017). Experimental studies suggest that neural and mesenchymal SCs could act to directly replace cells (*e.g.*, oligodendrocytes and neurons) and myelin (Jadasz et al., 2012; Meamar et al., 2016). Additionally, SCs can also produce immunomodulatory and trophic factors, with neuroprotective, regenerative, and growth properties (Reekmans et al., 2012; Teixeira et al., 2013; Meamar et al., 2016). The exact mechanisms by which SCs improve EAE

outcomes are unclear, but may favor activation of endogenous repair mechanisms (Reekmans et al., 2012). For example, SCs can activate endogenous cells to undergo growth or differentiation, and support other functions such as remyelination (Jadasz et al., 2012; Meamar et al., 2016). Among the many factors produced by mesenchymal SCs, brain derived neurotrophic factor is thought to support remyelination (KhorshidAhmad et al., 2016), promote survival of neurons/terminals, enhance neurite outgrowth (Crigler et al., 2006; Cova et al., 2010; Hsieh et al., 2013), and promote mitochondrial function (Markham et al., 2004, 2012, 2014). These functions fit nicely into the category of providing metabolic support for neurons and/or oligodendrocytes as a potential therapeutic mechanism. Thus, these multiple properties of SCs would be predicted to ameliorate the putative pathogenic mechanisms of progressive MS.

Conclusions

Therapies that support myelin maintenance, facilitate remyelination, and/or promote metabolism could in theory act to counter disease progression and possibly even help restore some small levels of function in some patients with progressive MS. Maximal benefit would be expected to come from an intervention that is started early in the course of progressive disease, including during the transition period from RRMS to SPMS, which may even help forestall the full conversion to SPMS. In patients with advanced progressive MS, where considerable pathology has accumulated (*e.g.*, extensive loss of axons and neurons), it will be more challenging for interventions targeting metabolism or remyelination to make a meaningful impact.

To achieve maximum benefit from metabolic therapies, multiple steps along biochemical pathways likely will need to be targeted as a deficiency in one step could undermine the effects of the intervention at a different step. A sub-optimal level of a nutrient could also limit responses in a trial of a test compound directed at a different facet of the pathogenic process, and a multifaceted approach with therapies that target other pathogenic mechanisms, *e.g.*, ocrelizumab acting on B cells, is predicted to give a better outcome than a therapy limited to only metabolic support.

In summary, therapies that support metabolism may be useful for treating patients with progressive MS. Maximal gains in the battle against this disease will likely come from a combination of therapies that are started early in the course of disease and promote repair, counter the disease process, and provide optimal support of oligodendrocyte and neuronal structures and functions.

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